A COMPARATIVE STUDY OF MICRO NUTRIENTS STATUS BETWEEN GESTATIONAL DIABETICS AND NORMAL PRIMI GRAVIDA

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DEPARTMENT OF PHYSIOLOGY

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COIMBATORE – 14

CERTIFICATE

This dissertation entitled **"A COMPARATIVE STUDY OF MICRO NUTRIENTS STATUS BETWEEN GESTATIONAL DIABETICS AND NORMAL PRIMI GRAVIDA"** is submitted to The Tamilnadu Dr.M.G.R Medical University, Chennai, in partial fulfillment of regulations for the award of M.D. Degree in Physiology in the examinations to be held during MAY 2018.

This dissertation is a record of fresh work done by the candidate **Dr.M. JEYALAKSHMI,** during the course of the study (2015 – 2018). This work was carried out by the candidate herself under my supervision.

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I, **Dr.M. JEYALAKSHMI** solemnly declare that the dissertation entitled **"A COMPARATIVE STUDY OF MICRO NUTRIENTS STATUS BETWEEN GESTATIONAL DIABETICS AND NORMAL PRIMI GRAVIDA"** was done by me at Coimbatore Medical College, during the period from July 2016 to June 2017 under the guidance and supervision of **Dr.D.SELVAM. M.D.,DCH.,** Associate Professor, Department of Physiology, Coimbatore Medical College, Coimbatore.

This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch - V) in Physiology. I have not submitted this dissertation on any previous occasion to any University for the award of any degree.

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CERTIFICATE – II

This is to certify that this dissertation work titled **A COMPARATIVE STUDY OF MICRO NUTRIENTS STATUS BETWEEN GESTATIONAL DIABETICS AND NORMAL PRIMI GRAVIDA** of the candidate **Dr.M.JEYALAKSHMI** with registration Number **201515253** for the award of **Doctor of Medicine** in the branch of **PHYSIOLOGY**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **1%** percentage of plagiarism in the dissertation.

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A COMPARATIVE STUDY OF MICRO NUTRIENTS STATUS BETWEEN GESTATIONAL DIABETICS AND NORMAL PRIMI GRAVIDA

CONTENTS

ABBREVIATIONS USED IN THE STUDY

GDM	-	Gestational Diabetes Mellitus
Zn	-	Zinc
Mg	-	Magnesium
OGTT	-	Oral Glucose Tolerance Test
IDDM	-	Insulin Dependent Diabetes Mellitus
NIDDM	-	Non Insulin Dependent Diabetes Mellitus
DM	-	Diabetes Mellitus
NGT	-	Normal Glucose Tolerance
IGT	-	Impaired Glucose Tolerance
IFG	-	Impaired Fasting Glucose
GLUT 2	-	Glucose Transporter 2
IRS	-	Insulin Receptor Substrate
IRTK	-	Insulin Receptor Tyrosine Kinase
OG	-	Obstetrics and Gynecology
ADA	-	American Diabetes Association
WHO	-	World Health Organization
CDC	-	Centre for Disease Control
BMI	-	Body Mass Index
ATP	-	Adenosin Tri Phosphate
PCOD	-	Poly Cystic Ovarian Disease
LMP	-	Last Menstrual Period
GA	-	Gestational Age
PP	-	Post Partum
ICF	-	Intra Cellular Fluid
ECF	-	Extra Cellular Fluid.

INTRODUCTION

INTRODUCTION

Gestational diabetes mellitus (GDM) is a metabolic disorder in pregnancy. It is defined as glucose intolerance that begins or is first recognized during pregnancy. Its prevalence varies from 4.6% to 9.2% around the world (CDC 2014). Moreover it was more prevalent in urban areas. GDM not only a risk factor for adverse perinatal outcome also for the development of type 2 diabetes mellitus.

The exact cause for GDM is not clearly known. It is characterized by insulin resistance and / or decreased insulin secretion. There are several predisposing factors for diabetes such as age, ethnicity, obesity, family history of diabetes. GDM is usually starts in middle and late gestational period and continues to term. Impaired glucose tolerance is more critical especially at the beginning of the second trimester of pregnancy [1].

Normal pregnancy is a state of insulin resistance. Many maternal hormones and factors play a role in causation of insulin resistance during pregnancy. In healthy pregnant women insulin resistance is compensated by pancrease, but in GDM women there is a impaired beta cell function. Insulin resistance during pregnancy due to alteration in the hormonal level such as growth hormone, cortisol, human placental lactogen and insulinase secretion. During pregnancy the imbalance between insulin resistance and secretion may lead to hyperglycemia. Undesirable effects of hyperglycemia

and GDM include premature delivery, dystocia, macrosomia, neonatal hypoglycemia etc [2].

There are many evidences on association between hyperglycemia and metabolism of minerals. Though macro elements are important nutrients for the body, trace elements also perform an essential role in various metabolic processes. Adequate maternal nutrition before and during pregnancy is imperative to the health of both mother and child. The metabolism of several minerals has been reported to alter in diabetes mellitus and these elements might have specific role in the pathogenesis and progress of the disease. Among these Zinc and Magnesium are essential trace elements with wide range of functions in the body. They are important for the growth and biological functions. They act as a cofactors for many metabolic reactions and play a vital role in basic cellular reactions required to maintain energy production and life.

Zinc an essential trace element is useful in the synthesis, storage, and secretion of insulin. Zinc as a trace element has indispensible role in human health and diseases. Zinc is found as component of more than 300 enzymes and plays a vital role in the maintenance of immune functions, many fundamental activities of cellular metabolism, taste sensation. Function of zinc can be categorised into catalytic, structural, and regulatory. Zinc deficiency affects about 2.2 billion people around the world. As biosystems

are unable to store zinc, regular intake is necessary . Zinc deficiency can be acute (diet poor in zinc), or chronic (inadequate absorption) [3].

In the mammalian pancreatic beat cell, zinc is essential for processing , storage, secretion and action of insulin. Insulin is stored in the secretory vesicles or granules, where two ions of zinc combines with six monomers of insulin and form hexameric structure of insulin. Changes in zinc levels in pancrease have been found to be associated with diabetes. Crystallographic studies have demonstrated the presence of zinc in crystals of insulin confirming the close relationship between zinc and insulin [1].

The name magnesium originate from Greek word - magnesia. The important interaction between phosphate and magnesium makes magnesium essential to the basic nucleic acid chemistry of all cells. Serum levels are typically 1.8 - 2.4 meq / L. Serum magnesium levels may be normal even when intracellular magnesium is deficient. Low plasma magnesium is common, the primary cause of deficiency is low dietary intake. Magnesium has an important role in insulin action, and insulin stimulates magnesium uptake [3] .

Plasma and intracellular magnesium concentrations are regulated by insulin and other factors. Lower intracellular magnesium concentration may result in a defective tyrosine kinase activity at the insulin receptor level and increase the intracellular calcium concentration. This will result in impairment of insulin action and a worsening of insulin resistance. Meta

analysis of thirteen prospective cohart studies involving 536318 participants detected a significant inverse association between magnesium intake and risk of type 2 diabetes mellitus. Of 536318 participants 24516 cases of DM were detected [4] . Since magnesium is an intracellular cation, it is very difficult to measure without invasive techniques. Serum magnesium levels can be measured but it does not necessarily reflect the more important intracellular concentration. Although magnesium deficiency is often reflected by low serum concentration deficiency often exists even with normal serum levels.

In developing countries where diet is monotonous and deficient in trace elements pregnant women are at increased risk of magnesium and zinc deficiencies. This is aggravated by increased demand for these trace elements to meet both the maternal and foetal needs. Some studies have shown that micronutrient deficiency is one of the serious issues in gestational diabetes mellitus. Other studies have shown that no deficiency of zinc, magnesium level in gestational diabetes women. The aim of the present study is to determine the serum levels of zinc, magnesium in GDM primi and to compare with normal pregnant women.

AIMS AND OBJECTIVES

AIM:

To compare the serum micronutient (zinc, magnesium) concentration in primigravida with gestational diabetes mellitus and normo glycemic primigravida.

OBJECTIVES:

- To estimate the serum magnesium and zinc levels in primigravida women with gestational diabetes mellitus.
- To estimate the levels of serum zinc, magnesium in normal primi women.
- To compare the concentrations of zinc and magnesium between women diagnosed with GDM and normal primigravida.
- To find correlation between blood sugar levels and serum zinc, magnesium concentrations in GDM.

REVIEW OF LITERATURE

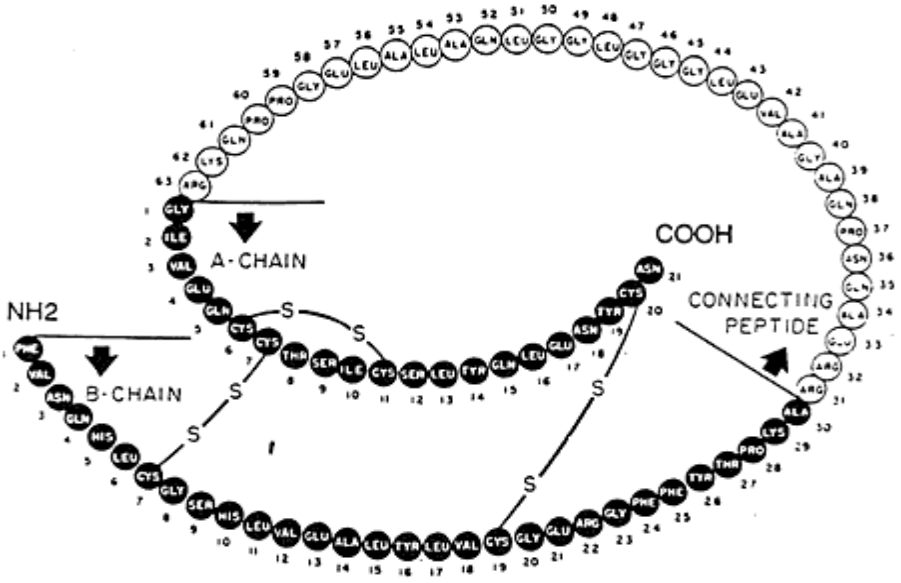
REVIEW OF LITERATURE

INSULIN

INTRODUCTION:

Insulin hormone is a 51 residue anabolic protein, plays a important role in regulation of metabolism. It is secreted by beta cells of islets of langerhans of pancreas. In 1916 Schafer first speculated that an Antidiabetic hormone, which he named insuline.

STRUCTURE :



Insulin was the first peptide hormone discovered. Sequence of human insulin is identical to that of porcine insulin except Ala B30 to Thr30 in human insulin. Primary sequence of insulin as determined by Sanger, insulin was a two chain heterodimer consisting of a 21 residue A chain linked to a 30 residue B chain by two disulfide bonds[1].

FREDERICK SANGER

BIO SYNTHESIS:

In humans, the short arm of chromosome 11 contains the gene for preproinsulin, which is the precursor of insulin. Its coding region consists of 3 exons, Transcription and splicing to remove the sequences encoded by introns yields a messenger RNA of 600 Neucleotide, transulation of which gives rise to preproinsulin. Preproinsulin is rapidly discharged into cisternal space of rough endoplasmic reticulum, where proteolytic enzymes immediately clear the single peptide, generating proinsulin.

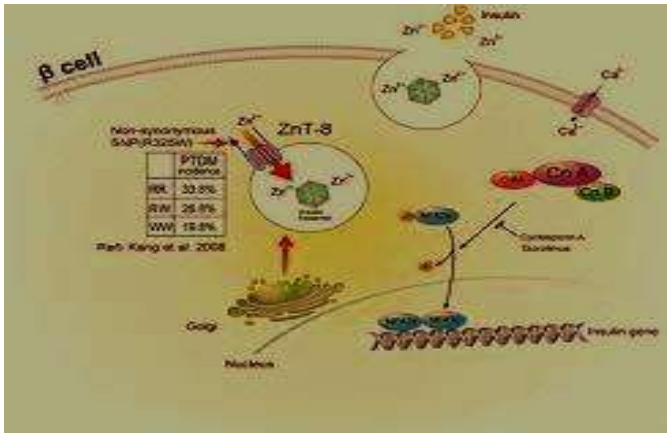
The structural conformations of proinsulin & insulin are very similar and a major function of the c- peptide is to align the disulfide bridges that link the A & B chains so that the molecule is correctly bolded for cleavage. Proinsulin is transported in microvesicle to the golgi apparatus, where it is packaged into membrane – bound vesicles known as secretary granules. The conversion of proinsulin to insulin is initiated in Golgi Complex and continues within the maturing secretary granule through the sequential action of a endopeptidases (Prohormone convertase 2 & 3) and carboxypeptidase H, which remove the C- peptide chain, liberating two cleavage dipeptides and finally yielding insulin.

Insulin and C-peptide are stored together in the secretary granules and are ultimately released in equimolar amounts by a process of regulated exocytosis. Under normal conditions > 95 % of secreted product

is insulin & < 5 % release as proinsulin. However secretion of incompletely processed insulin precursors is increased in some patients with type 2 diabetes.

β cell responds to increases in the circulating concentrations of nutrients by increasing insulin production and secretion, thus maintaining insulin stores. Acute (<2 hours) increase in Extracellular concentration of glucose & other nutrients result in a rapid and dramatic increase in the transcription of preproinsulin mRNA and in the rate of proinsulin synthesis. There is a sigmoidal relationship between glucose concentration & bio synthetic Activity, with a threshold glucose level of 2 to 4 mmol / L. This is slightly lower than the threshold for the stimulation of insulin secretion which ensures an adequate reserve of insulin within the β cell [1].

INSULIN STORAGE:



Insulin becomes associated with zinc as the secretory granules mature. Newly synthesised insulin likely to form crystals with zinc that are transported into mature secretory granule. In the presence of zinc, insulin dimers associate to form hexameric units co-ordinated by 2 zn ions within central axis of hexamer. The zinc - insulin crystals form the dense central core of the granules, whereas C- peptide is present in the clean space between granule membrane and core. The insulin secretary granule has a typical appearance in electron micrographs, with a wide space between the crystalline electron – opaque core and its limiting membrane. The major protein constituents of the granules are insulin and C- peptide.

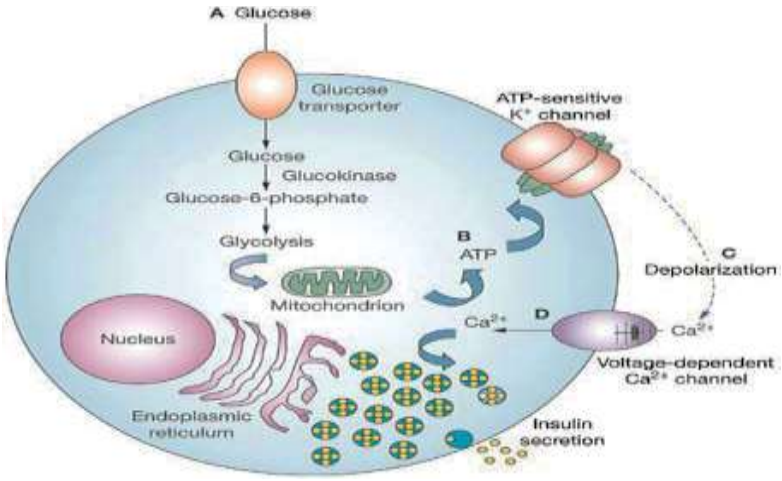
Microtubules are formed by the polymerization of tubulin subunits and normally form a network radiating outwards from the perinuclear region. The microtubular network is in a process of continual remodeling and the dynamic turnover of tubulin rather than the total number of microtubules is important for the mechanism of secretor . The microtubule framework may provide the pathway for the secretory granules but microtubules do not provide the motive force. So other contractile proteins are likely to be involved. Actin is the constituent protein of microfilaments which exist in cells as a globular form and as a filamentous form which associates to form microfilaments.

Microfilament Polymerization is regulated by agents that alter rates of insulin secretion and the pharmacologic disruption of microfilament formation

inhibits insulin secretion. myosin light and heavy chains are expressed at high concentrations in β cells, suggesting that acting & myosin may interact to propel granules along the micro tubular network. It also seems likely that other molecular motors, including kinesin & dynein are also involved in movement of secretory granules & perhaps other organells in β cells.

Insulin is released from secretory granules by exocytosis, a process in which the granule membrane and plasma membrane fuse together, releasing the granule contents into the interstitial space. Much of knowledge of the molecular mechanisms of exocytosis is derived from studies of Neurotransmitter release from nerve cells, and similar mechanism operate in β cells [1].

SECRETION:



Blood glucose is the major stimulant for insulin secretion. Secretion of insulin is not only an important step in regulation of glucose homeostasis in healthy individuals but has also been demonstrated to be impaired in both type 1 and type 2 diabetes mellitus. Only a small portion

of insulin stored in vesicles released, even under maximum stimulation, this suggests that insulin levels are regulated by secretion rather than by synthesis and is not ordinarily limited by size of storage pools[1] .

EFFECT OF INSULIN:

Insulin receptor is a protein kinase receptor that contains enzyme activity. Once insulin arrives at the target cell, it binds with the insulin receptor (alpha chain) activates tyrosine kinase activity of the beta chains. The IRS tyrosine phosphorylations are followed by various cascades of events that ultimately produce gene expression, Translocation of glucose transport proteins to the plasma membrane, activation or deactivation of numerous enzymes in glucose and fatty acid metabolism and protein synthesis.

Insulin increases uptake of glucose in target cells (muscles, adipose tissue, leucocyte, mammary gland) by translocating the glucose transporter into the cell membrane. Tissues in which glucose transport is not insulin dependent include nervous system, kidney, RBC, retina, blood vessels, and intestinal mucosa [1].

DIABETES

The prevalence of diagnosed diabetes among American adults has increased by 40% in 10 years & rose from 4.9% in 1990 to 6.9% in 1999.

More worryingly, it is estimated that this incidence will increase another 165% by 2050, to put this into perspective the lifetime Risk of diabetes in individuals born in 2000 is 33% for males & 39% for females [2].

Increasing prevalence of type 2 Diabetes particularly in younger people in particular has led to an increasing number of pregnancies with complications. Many women found to have gestational diabetes are likely to have type 2 Diabetes that has previously gone undiagnosed. Indeed the incidence of Diabetes complicating pregnancy has increased approximately 40% between 1989 and 2004. There is keen interest in events that precede diabetes and this includes the mini – environment of uterus, where it is believed that early imprinting can have effects later in life. For example, In utero exposure to maternal hyperglycemia leads to fetal hyperinsulinemia, causing an increase in fetal fat cells which leads to obesity and insulin resistance in childhood. This in turn leads to impaired glucose intolerance & diabetes in adulthood. Thus a cycle of fetal exposure to diabetes leading to childhood obesity & glucose intolerance is set in motion. This sequence has been reported in pima Indians as well as a heterogenous Chicago population [2].

CLASSIFICATION

Diabetes is now classified based on the pathogenic processes involved. Absolute insulin deficiency characterizes type I diabetes, whereas defective insulin secretion or insulin resistance characterizes type 2 Diabetes. The terms

IDDM & NIDDM are no longer used. Age is also no longer used in classification because pancreatic β cell disfunction can begin at any age. Most commonly its onset is before age 30 but in 5 to 10% of affected individuals, onset is after age of 30 years. Type 2 diabetes, although most typical with increasing age also develops in obese adolescents [2].

CLASSIFICATION DURING PREGNANCY

Diabetes is the most common medical complication of pregnancy . Women can be separated into those who were known to have diabetes before pregnancy -- Pregestational or overt and those diagnosed diabetes during pregnancy are gestational. In 2006, Slightly more than 1,79,898 American women had pregnancies complicated by some form of diabetes, representing 4.2% of all live births. In the United States, African – Americans, Native Americans, Asians and Hispanic women are at higher risk for gestational diabetes compared with white women. The incidence of Gestational Diabetes over the past 15 years was increased [2].

ETIOLOGICAL CLASSIFICATION OF DIABETES MELLITUS

1. Type 1

β cell destruction, usually absolute insulin deficiency

A - Immune mediated

B - Idiopathic

2. Type 2

Ranges from predominantly Insulin Resistance to predominantly an Insulin Secretory defect with Insulin – Resistance .

3. Other types

A – Genetic mutation of β cell function

B – Genetic defects in insulin action

C – Genetic syndromes (Down, Klinefelter, Turner)

D – Disease of exocrine pancreas (Pancreatitis / Cystic.Fibrosis)

E – Endocrinopathies (cushing syndrome, pheochromocytoma)

F – Drug or chemical induced (Glucocorticosteroid/ Thiazides / β adrenergic agonist).

G – Infection (Congenital Rubella, CMV, Coxsackie Virus).

4. GDM.

GESTATIONAL DIABETES

Carbohydrate intolerance of variable severity with onset or first recognition during pregnancy is known as gestational diabetes mellitus. This definition applies whether or not insulin is used for treatment. Undoubtedly Some women with gestational diabetes have previously unrecognized overt diabetes. Sheffield and co- workers studied outcomes in 1190 diabetic women delivered at parkland hospital between 1991 and 1995. They found that women with fasting hyperglycemia diagnosed before 24weeks had pregnancy outcomes similar to those for women overt diabetes. Bartha & most with their colleagues reported similar results. Thus, fasting hyperglycemia early in pregnancy almost invariably represents overt diabetes [2].

SCREENING

Despite more than 40 yrs of Research, there is no consensus regarding the optimal approach to screening for Gestational Diabetes. The major issues include whether universal or selective screening should be used and which plasma glucose level after a 50 – g glucose test threshold is best to identify women at risk for GDM.

Screening should be performed between 24 and 28 weeks in those women not known to have glucose intolerance earlier in pregnancy. This evaluation is usually done in 2 steps. In the 2 step procedure, a 50g – oral

glucose challenge test is followed by a diagnostic 100g OGTT, if initial results exceed a predetermined plasma glucose concentration.

Plasma glucose level is measured one hour after a 50 g glucose load without regard to the time of day or time of last meal. A value of $\geq$ 140 mg / dl identifies 80% of all women with Gestational Diabetes using a value of $\geq$ 130 mg / dl increase the yield to greater than 90%. However 20 – 25% of women will have false positive test results compared with only 14 to 18% when the $\geq$ 140 cut of value is used.

The day – to day reproducibility of the 50 g – screening test has been evaluated by Espinosa de los Monteros and Co – workers. Although 90% of normal results were reproducible the next day, only 83% of abnormal test results were reproducible. Murphy & colleagues studied the accuracy & Precision of Reflectance Photometers. Accucheck III – for Screening because this required redefining the circumstances for Testing & threshold values for abnormal results, it seem best to avoid these devices for screening. Gabbe & associates surveyed practicing OG in 2003 & reported that 96% used universal screening for Gestational diabetes. Integral to Justifying this practice is the requirement to show that women who screen positive are benefited by the treatment [2].

MATERNAL & FETAL EFFECTS

Adverse fetal consequences of diabetes varies in women with gestational diabetes than in women with overt diabetes, fetal anomalies are not increased. Similarly, pregnancies in women with overt diabetes are at greater risk for fetal death. This danger is not apparent for those who have diet – treated post prandial hyperglycemia.

In contrast, women with elevated fasting glucose levels have increased rates of unexplained still births similar to women with pre gestational diabetes specifically the American Diabetes association has concluded that fasting hyperglycemia > 105 mg/dl may be associated with an increased risk of fetal death during the last 4 – 8 weeks of gestation. Adverse maternal effects include an increased frequency of hypertension & cesarean delivery [2].

MANAGEMENT

Women with gestational diabetes can be divided into 2 functional classes using fasting glucose levels. Insulin therapy is usually recommended when standard dietary management does not consistently maintain the fasting plasma glucose at < 95 mg / dl or 2 hr Postprandial plasma glucose < 120 mg/ dl. Whether insulin should be used in women with lesser degree of fasting hyperglycemia – 105 mg/dl or less before dietary intervention is unclear because there have been no controlled trials to

identify ideal glycemia targets for prevention of fetal risks. The fifth international workshop conference on GDM, however recommended that maternal capillary glucose levels be kept $\leq$ 95mg/dl in the fasting state [2].

DIET

ADA has recommended nutritional counseling with individualization based on height & weight and diet that provides an average of 30 kcal / kg / day based on pregnant bodyweight for non-obese women. Although the most appropriate diet for women with GDM has not been established, the ADA has suggested that obese women with a BMI > 30 kg / m^2 may benefit from 30% caloric restriction and should be monitored with weekly tests for ketonuria, because maternal ketonemia, has been linked with impaired psychomotor development in offspring. Langer & colleagues found that insulin was necessary to achieve glucose control in obese women [2].

EXERCISE

Because exercise is known to be important in non- pregnant Patients, the American college of O & G reviewed 3 Randomized Trials of exercise in women with GDM. The results suggested that exercise improved cardio respiratory fitness without improving pregnancy outcome. Dempsey & coworkers found that physical activity during pregnancy reduced the risk of

gestational diabetes. Brankston & associates reported that resistance exercise diminished the need for insulin therapy in overweight women with GDM [2].

GLUCOSE MONITORING

Hawkins & colleagues compared outcomes in 315 women with diet – treated gestational diabetes who used personal glucose monitors with those of 615 women with GDM who were also diet - treated but who underwent glucose evaluation intermittently during obstetrical visits only. Women using daily self-blood glucose monitoring had fewer macrosomic infants & gained less weight after diagnosis- median 0.56 compared with 0.74 pounds per week – then women evaluated during clinic visits only. These researcher's findings support the common practice of self blood glucose monitors for women with GDM who are treated with diet alone.

Postprandial surveillance for GDM has been shown to be superior to pre-prandial surveillance. Devecians & colleagues studied 66 pregnant women with Class A2 diabetes in whom insulin was initiated for fasting hyperglycemia. The women were randomized to glucose surveillance Using either pre-prandial or 1 hour Postprandial capillary blood glucose concentration measured by glucometer. Postprandial surveillance was shown to be superior in that blood glucose control was significantly improved & was associated with fewer causes of neonatal Hypoglycemia 3 versus 21%

less macrosomia 12 versus 42 % & fewer cesarean deliveries for dystocia 24 versus 39% [2].

INSULIN

Insulin given to decrease the complications related to macrosomia in women with GDM & fasting euglycemia has long been controversial. Langer & co -workers reviewed 23 reports from 1979 through 1993 & found that none demonstrated improved prenatal outcomes related to any management approach, including prophylactic insulin treatment. Four Randomized studies reported between 1989 & 2001 showed that intensive therapy had little effect on birthweight, birth Trauma, operative delivery or neonatal complications.

Most practitioners - 93 % According to Owen & colleagues initiate insulin therapy in women with GDM if fasting glucose level exceeding 105 mg/ dl persist despite diet therapy. A total dose of 20 – 30 unites given once daily before breakfast is commonly used to initiate therapy. The total dose is usually divided into 2/3 intermediate acting insulin & a third short acting insulin. Alternatively, weight based split dose insulin is administered twice daily. Once therapy has been initiated, it must be recognized that the level of glycemic control to reduce fetal & neonatal complications has not been established [2].

OHA: (Oral Hypoglycemic Agent)

The American College of O & G has not recommended these agents during pregnancy. Langer & Colleagues randomized 404 women with GDM to insulin versus glyburide therapy. Near normoglycemia levels were achieved equally well with either regimen and there were no apparent neonatal complications attributable to glyburide. In a follow-up study Conway & co-workers reported that women with fasting glucose levels > 110 mg/dl did not adequately respond to glyburide therapy. Similar results were reported by Chmait & Kahn and their associates. Until recently, glyburide was thought not to cross the placenta, Hebert & colleagues, howeller sampled 20 paired maternal & umblical specimens and found umblical cord concentrations were half that of maternal concentration in women treated with glyburide.

There is increasing support for the use of glyburide as an alternative to insulin in the management of gestational diabetes. A survey of almost 1400 fellows of American college of O & G found that 13 % of respondents were using glyburide as 1^{st} line therapy for diet failure with GDM. Further evidence of expanding use of glyburide was provided by Kremer & Jacobson and their colleagues. They reported glyburide as an alternative to insulin . Most of these women required daily glyburide doses < 7.5 mg to achieve glucose control. Hypoglycemia was reported to be less frequent when glyburide was compared with insulin. In a recent meta – Analysis, moretti &

Associates reported no increased perinatal risks with gluburide therapy and recommended further randomized trials.

Metformin has been used as treatment for polycystic Ovarian Disease and has been reported to reduce the incidence of GDM in women who use the drug througout pregnancy. The 5th international workshop conference recommended that metformin treatment for GDM be limited to clinical Trials with long term infant follow –up [2].

OBSTETRICAL MANAGEMENT

In general women with GDM who do not require insulin seldom require early delivery or other interventions. Elective cesarean delivery to avoid brachial plexus injuries in macrosomic infants is an important issue. American college of O & G has suggested that cesarean delivery should be considered in women with a sonographically estimated Fetal weight $\geq$ 4500g. Effects of such a policy were retrospectively analysed by Gonen & Colleagues in a general obstetrical population of >16000 women. Elective ceasaren delivery has no significant effect on incidence of brachial plexus injures.

Elective induction to prevent shoulder dystocia in women with sonographically diagnosed fetal macrosomia compared with spontaneous labour is also controversial. Conway & Langer found that elective delivery

reduced the rate of shoulder dystocia from 2.2 to 0.7%. In constrast, charhan & co-workers reviewed the literature and concluded that sonographic suspicion of macrosomia was too inaccurate to recommend induction or primary cesarean delivery without a trial of labour. There is no consensus regarding whether antepartum fetal testing is necessary and if so, when to begin such testing in women without severe Hyperglycemia [2].

POST PARTUM EVALUATION

The 5th International workshop conference on gestational diabetes recommended that women diagnosed with gestational diabetes undergo evaluation with a 75g oral glucose tolerance test at 6- 12 weeks postpartum & other intervals thereafter. Although Postpartum follow –up of women diagnosed with GDM was recommended for PP follow up are based, on the 50 % likelihood of women with GDM developing overt diabetes within 20 years. If there is fasting Hyperglycemia then Diabetes is more likely to persist postpartum. For Example in women with fasting glucose levels of 105 to 130 mg/d1, 43 % were found to be overtly diabetic, when fasting glucose exceeded 130mg/dl during pregnancy, 86 % became overtly diabetics.

Likewise insulin therapy during pregnancy and especially before 24 weeks is a powerful predictor of persistent diabetes. Women with a history of gestational diabetes are also at risk for cardiovascular complications

associated with dyslipidemia, hypertension and abdominal Obesity – the metabolic syndrome. Pallardo and colleagues evaluated cardiovascular disease risk factors 3-6 months PP in 788 women with GDM. They found that the degree of PP Glucose inloterance was significantly associated with these risk factor. A recent Canadian study by Shah & coworkers documented excessive cardiovascular disease even by 10 years in these women compared with non-diabetic controls. Finally Akinci & Associated reported that a Fasting glucose level $\geq$ 100mg/dl with index OGTT was an independent predictior of metabolic syndrome.

Recurrence of GDM in subsequent pregnancies was documented in 40% of 344 primiparous women analysed by Holmes and colleagues. Obese women were more likely to have impaired glucose intolerance in subsequent pregnancies. Thus lifestyle behavioural changes including weight control and exercise between pregnancies likely would prevent recurrence of GDM as well as modify onset and severity of type 2 DM later in life. Interestingly perinatal outcome in women with previous GDM but with normal glucose tolerance test during a subsequent pregnancy were not improved with regard to birth weight / macrosomia, route of delivery and neonatal complication. Finally women without GDM in their first pregnancy were unlikely to have GDM when screened in a 2nd pregnancy [2].

ZINC RICH FOOD

ZINC :

Total zinc content of body is about 2 g out of which 60 % in Skeletal muscle and 30 % in bones. Zinc is mainly an intracellular element. Highest concentration of zinc is seen in hippocampus area of brain and prostatic secretion.

HISTORY:

In 1974, NAS (National Academy of Sciences) declared zinc to be an essential element for humans and established a recommended daily allowance.

In 1978, FDA (Food & Drug Administration) required zinc to be in total parenteral nutrition fluids.

In 2002 ZIP4 (Zinc Transporter) was first identified as the mechanism for absorption of zinc in the gut across the basolateral membrane of enterocyte. Zinc may have an effect on cancer and further study is recommended.

SOURCES:

Rich dietary sources are grain, beans, nuts, cheese, meat, shellfish, egg, and milk.

ABSORPTION:

Zinc is absorbed mainly in duodenum. Zinc from the animal sources is better absorbed than the vegetable sources. Zinc absorption appears to be dependent on a transport protein metallothionein.

METALLOTHIONEIN:

It is a cysteine rich, low molecular weight protein. It was discovered in 1957 by vallee & margoshe. It has four isoforms. In human, large quantities are synthesised primarily in the liver & kidney. Production is depend on availability of dietary minerals such as zinc, copper, selenium. It is involved in zinc and copper regulation. Metallothionein participate in uptake, transport and regulation of zinc in biological systems. By binding and releasing zinc, metallothionein may regulate zinc levels within the body.

Phytate, calcium, copper and iron interfere with zinc absorption, while small peptides and aminoacids promotes zinc absorption. Zinc and copper will competitively inhibit each other’s absorption. So zinc is therapeutically useful to reduce copper absorption in wilson's disease.

In liver, zinc is stored in combination with a specific protein, metallothionein. zn is excreted through pancreatic juice and to a lesser extent through sweat [3].

SERUM ZINC:

The concentration of zinc in serum is about 100 mg / dl. Erythrocytes contain higher content of zinc about 1.5 mg / dl, which is found in association with the enzyme carbonic anhydrase [3].

COLORIMETRIC METHOD:

For the determination of Zinc in serum and urine.

Method : Nitro - PAPS

Nitro - PAPS is a highly sensitive colorimetric reagent, used for direct determination of serum iron or other metals.

CHEMICAL NAME :

2 - (5- Nitro - 2 - Pyridylazo) - 5 - (N - n - propyl - N - (3 - sulfopropyl) Amino phenol, disodium salt, dihydrate.

$C_{17}H_{19}N_5Na_2O_6S.2H_2O$.

PRINCIPLE:

Zinc is an alkaline medium reacts with Nitro-PAPS to form a purple coloured complex. Intensity of the complex formed is directly proportional to the amount of zinc present in the sample.

Zinc + Nitro PAPS ------ purple coloured complex.

Normal reference value:

Serum : 60 - 120 µg / dl

Urine : 100 - 1000 µg / 24 hours.

REQUIREMENTS :

For adult - 10mg / day

children - 10mg / day

In pregnancy and lactation - 15 to 20 mg / day .

Since iron inhibits absorption of zinc, when iron is supplemented, zn is also to be given to prevent zn deficiency [3].

BIOCHEMICAL FUNCTION :

1. Zinc is an essential component of several enzymes. eg: Carbonic anhydrase, alcohol dehydrogenase, alkaline phosphatase, carboxy peptidase, superoxide dismutase.

2. Zinc may be regarded as an Antioxidant since the enzyme superoxide dismutase protects the body against free radical damage.

3. The storage and secretion of insulin from the Beta cells of pancreas require zinc.

4. Zinc is necessary to maintain the normal level of vitamin A in serum. Zn promotes the synthesis of retinol binding protein.

5. It is required for wound healing. Zinc enhances cell growth and division, besides stabilizing biomembranes.

6. Gusten, a zn containing protein of the saliva is important for taste sensation.

7. Zinc is essential for proper reproduction [3].

ZINC DEFICIENCY MANIFESTATIONS:

Zinc deficiency is associated with growth retardation, poor wound healing, Anemia, loss of appetite, loss of taste sensation, impaired spermatogenesis etc. It is reported that Zn deficiency in pregnant animals causes congenital malformations of the fetus. Deficiency of Zn may result in depression, dementia and other psychiatric disorders. The neuropsychiatric manifestations of chronic alcoholism may be partly due to zinc deficiency.

Acrodermatitis enteropathica is a rare inherited metabolic disease of Zn

deficiency caused by a defect in the absorption of zn from the intestine [3].

ZINC TOXICITY :

Toxic manifestation are seen when intake is > 1000 mg / day. Toxicity of zn is usually seen in welders due to inhalation of zinc Oxide fumes. Many rat poisons contain zn compounds which lead to accidental poisoning.

Chronic toxicity may produce gastric ulcer, pancreatitis, Anemia, Nausea, vomiting & Pulmonary fibrosis. Acute Toxicity is manifested as fever, excessive salivation, headache & Anemia [3].

ZINC AND INSULIN:

Zinc affects insulin signaling pathway. zinc potentiates the mitogenic signaling of insulin, and activates extra cellular signal regulated kinases 1 & 2. Zinc has an insulin like effect. Coulston & Dandona first reported that Zn promoted lipogenesis of rat epididymal adipocytes through a post insulin receptor mechanism. To help explain the results of transport, the phosphorylation state of several proteins in the insulin signaling pathway were assayed. First the effect of insulin and zinc on tyrosine

phosphorylation of 95- K Da insulin receptor beta subunit were investigated. Insulin increases tyrosine phosphorylation of IR-B subunit on both 3T3-L1, fibroblast and adipocytes. Zncl2 also produced an insulin like effect but extent was lower than that of insulin [5]. Lowered circulating level of zinc are also found in diabetes mellitus. Zinc ions are essential for a huge range of cellular funtions and in specialised pancreatic beta cell, for storage of insulin within the secretory granule. Studies have shown that zinc may play a role in improving peripheral insulin sensitivity, as it can potentiate insulin stimulated glucose transport [6].

Genome wide association studies have found, the islet- restricted zn transporter zn T 8 (SLC30A8) as a potential controller of insulin secretion and hence may modulate the risks of developing type 2 diabetes. Results show that post supplementary HbA1c values were significantly reduced in the zinc treated groups compared with controls [7].

It appears that the beneficial effects of zinc supplementation on metabolic parameters can be seen mainly in individuals with zinc deficiency or disease causing zinc deficiency such as diabetes. In addition to hypoglycemic and lipid lowering effect of regular zinc supplementation in patients with diabetes, results show that it reduces lipid peroxidation & hence demonstrate antioxidant effects. Thus it is possible to hypothesis that reduction in diabetes complication may be due to reduction of oxidative damage from zinc supplementation[8].

MAGNESIUM RICH FOOD

MAGNESIUM

The name Magnesium originates from the greek word for a district in thessaly called magnesia.

Magnesium is the fourth most abundant cation in the body and 2nd most prevalent intracellular cation. Magnesium is mainly seen in intracellular fluid (ICF). Total body mg is about 25g. 70 % of which is complexed with Calcium and phosphorous in bone. The remaining 30 % occurs in the soft tissues and body fluids. 1/3 of skeletal mg is exchangeable with serum [3] .

DIETARY REQUIREMENTS :

Adult man – 350 mg / day

Adult women – 300 mg / day

SOURCES :

Cereals/ nuts / beans / vegetables / cabbage / cauliflower / meat / milk / fruit.

ABSORPTION :

Magnesium is absorbed by the intestinal cells through a specific carrier system. About 50 % of the dietary mg is normally absorbed. Consumption of large amount of calcium, phosphate and alcohol diminishes mg absorption. PTH (para thyroid hormone) increases mg absorption.

NORMAL SERUM LEVEL OF MAGNESIUM :

Normal serum level mg is 1.8-2.2 mg /dl. Inside the RBC, the mg content is 5 meq / l . In muscle tissue mg is 20 meg / L about 70% of mg exists in free state and remaining 30% in Protein bound (25%Albumin & 5% to globulin). Serum must be separated from clot as soon as possible. Or the level of mg will increase because of its elution from the RBC. Hemolyzed sample as well as blood collected with citrate, oxalate or EDTA are unacceptable for analysis. Homeostasis is maintained by intestinal absorption as well as by excretion by kidney. Mg is reabsorbed from loop of henle and not from proximal tubule [3].

MODIFIED XYLIDYL BLUE REACTION METHOD:

It is a colorimetric method for magnesium estimation.

PRINCIPLE:

Magnesium determination is based on the reaction of magnesium with xylidyl blue 1 ac chelator at alkaline pH which yields a purple coloured complex.

FUNCTIONS

1. Magnesium is the activator of many enzymes requiring ATP. Alkaline phosphatase / hexokinase / Fundokinase, PFK/ adenyl cyclase/ cAMP dependent kinase, etc .
2. Neuro muscular irritability is lowered by magnesium.

3. Insulin dependent uptake of glucose is reduced in mg deficiency. Mg supplementation improves glucose tolerance [3] **.**

DISEASE STATES :

1. Magnesium deficiency causes neuromuscular irritation, weakness and convulsion. These symptoms are similar to that observed in tetany (Ca deficiency) which are relieved only by magnesium. Malnutrition, alcoholism and cirrhosis of liver may lead to mg deficiency.

2. Low level of mg may be observed in uremia, rickets & abnormal pregnancy.

HYPOMAGNESEMIA :

It is commonly seen in hospital patients. Conditions which require magnesium estimation are enumerated in table. When serum mg level falls below 1.7 mg /dl it is called hypomagnesemia. Vomiting / Nasogastric suction, diarrhoea, liver cirrhosis, protein – calorie malnutrition and diuretic

therapy are the common causes. Urinary loss can occur in alcoholism, osmotic diuretics, loop diuretics and Amino glycosides. Serum mg levels need not always reflect body content. measurement of urinary mg excretion will distinguish between renal and gastro intestinal losses.

Deficiency of magnesium leads to Neuromuscular hyperirritability and cardiac arrhythmias. The mg deficiency symptoms are similar to those of Ca deficiency but symptoms will be relieved only when mg is given. Acute symptomatic deficiency is treated by giving parenteral mg. Oral therapy may lead to diarrhoea hence i.v mg sulphate is given [3].

HYPERMAGNESEMIA :

It is uncommon and always due to excessive intake either orally (Antacids) rectally (enema) or parenterally. Magnesium intoxication causes depression of neuromuscular system causing lethargy, hypotension, respiratory depression, bradycardia and weak tendon reflex. In severe conditions acute Rhabdomyolysis results [3].

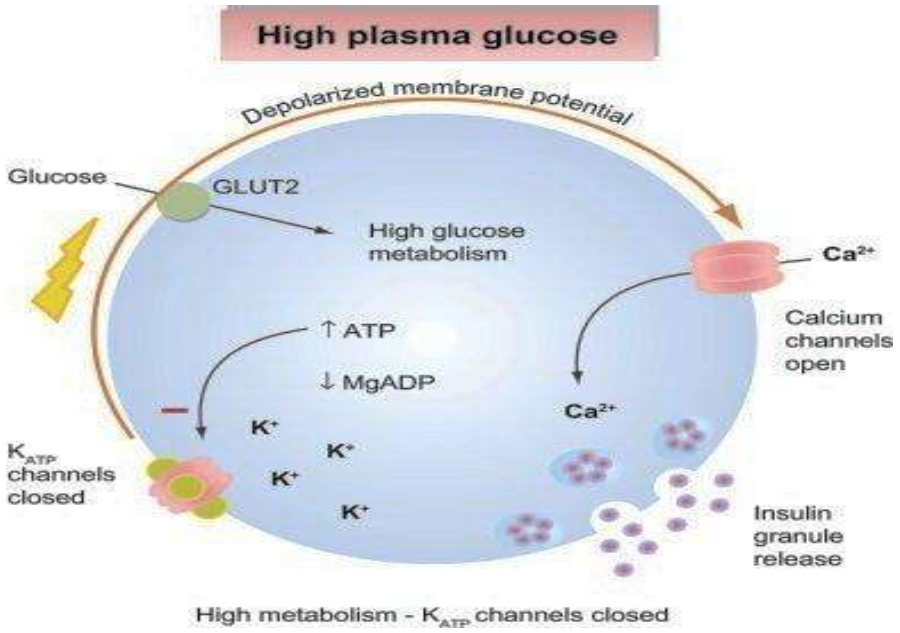
CAUSES :

Hypomagnesemia	Hypermagnesemia
1. Urinary loss (Tubular necrosis) 2. Hyperaldosteronism Volume expansion 3. Familtral hypomagensemia 4. Increased intestinal loss (Diarrhoea, laxatives, Ulcerative Colitis, Nasogastric suction. 5. Cirrhosis 6. Malabsorption 7. Protein calorie malnutrition 8. Hypoparathyroidism 9.Drugs: Thiazide,Aminoglycoside,Cisplatin Amphotericin,Cyclosporin, Haloperidol , Alcohol.	1. Excess intake orally 2. RenalFailure 3. Hyperparathyroidism 4. Oxalate poisoning 5. Rickets 6. Multiple myeloma 7. Dehydration 8. Drugs.

Magnesium is one of the most abundant ions present in living cells and its plasma concentration is remarkably constant in healthy subjects. Plasma and intracellular magnesium concentration are tightly regulated by several factors. Among them insulin seems to be one of the most important. In vitro & in vivo studies have demonstrated that insulin may modulate the shift of magnesium from extracellular to intracellular space. Intracellular magnesium concentration has also been shown to be effective in modulating insulin action mainly oxidative glucose metabolism. A poor

intracellular magnesium concentration as found in NIDDM patients may result in a defective tyrosine kinase activity at the insulin receptor level and is responsible for the impairment in insulin action and a worsening of insulin resistance in NIDDM. By contrast in NIDDM patients daily administration of magnesium restoring a more appropriate intracellular magnesium concentration contributes to improve insulin mediated glucose uptake. The benefits deriving from daily magnesium supplementation in NIDDM patients are further supported by epidemiological studies showing that high daily magnesium intake are predictive of a lower incidence of NIDDM. Intracellular magnesium may play a key role in modulating insulin mediated glucose uptake [9].

FUNCTION OF MAGNESIUM IN INSULIN SECRETION



Glucose is the important stimulator of insulin secretion from pancreatic beta cell. The first step in insulin secretion is their intracellular uptake of

glucose via GLUT 2. Glucose is metabolized via glycolytic pathway, tricarboxylic acid cycle, oxidative phosphorylation. Numerous enzymes in these metabolic pathways are dependent on magnesium.

FUNCTION OF MAGNESIUM IN INSULIN SIGNAL TRANSDUCTION

The binding of insulin to its receptor results in autophosphorylation and internalization. Internalized insulin receptors phosphorylate IRS 1 - 6. In these reactions mg is operating together with ATP as a kinase substrate. Additionally a second mg is bound to a regulatory site of insulin receptor tyrosine kinase [10].

MAGNESIUM IN OBESITY:

Insulin resistance may be caused by a reduced number of insulin receptors, by mutation of insulin receptors leading to reduced affinity of insulin binding or by reduced activity of IRTK. The most important risk factor in insulin resistance is obesity. It has been suggested that obesity induced insulin resistance involves an alteration in mg metabolism plus other mechanisms.

Obese Zucker fat rats were used as a model for the role of obesity in insulin resistance and type 2 diabetes. Magnesium supplementation of

obese rats resulting in a drop in the blood glucose concentration. These studies showed the inverse association between mg intake and metabolic syndrome. The probable effect of mg supplementation may be caused by high mg concentration in intestine, followed by increased fluid volume. Thus carbohydrates and enzymes are more diluted. Due to Hydrolysis of carbohydrates within the intestinal lumen, increase in plasma glucose in the mg supplementated obese zucker fat rats may be slower than in the controls [10].

MAGNESIUM IN INSULIN SECRETION AND INSULIN RESISTANCE IN HUMAN:

Magnesium supplementation in insulin requiring type 2 diabetic patients increased serum mg concentration from 0.78 to o.82 mM and did not improve glycemic control in a study. In another study mg supplementation of type 2 diabetic subjects increased serum magnesium concentration from 0.65 to 0.74 mM and induced a slight improvement in glycemia and HbA1c. It may be argued that the serum mg concentration must be significantly reduced to obtain improved insulin sensitivity and metabolic control by mg supplementation [10].

STUDY RELATED TO DIABETES / MICRO NUTRIENTS

In a Study done by Farideh Akhlaghi, in Iran, measured micronutrients (Ni, Al, Cr, Mg, Zn, Cu, Se) level in serum of gestational

diabetes found that no significant difference between study and control group [11].

In Nigeria Emmanuel I.Ugwuja done a study on plasma zinc, copper level in pregnant women with diabetes mellitus. He noted low serum zinc level in diabetic pregnant women, may be due to hyper excretion of zinc in urine- hyperzincuria. In hyperglycemia by interference with active transport of zinc into the renal tubular cells [12].

Study done by sae jeong yang et al in korea showed that the type 2 DM group with previous gesatational diabetes had the lowest serum magnesium level in the post partum period [13].

Study by fadia mahmoud showed that zinc level was lower in pregnant women than non pregnant women. but he found that no change in zinc level in gdm mother as compared to normal pregnant mother and significant increase in magnesium level [14].

Correlation of serum zinc, magnesium with type 2 DM patients was evaluated by Sunita pujar, in bagalkot. the level of serum zinc and magnesium was statistically significantly decreased in diabetes mellitus patients compared to healthy controls [15].

Mohammad Keshvari et al showed that serum magnesium, zinc concentration has significant difference between gestational diabetic and non diabetic pregnant women. serum zinc and magnesium levels of diabetics were less than non diabetic pregnant women [16].

Effect of zinc supplementation on insulin resistance was studied by Neda Roshanravan et al. according to the study there were no significant statistical changes in FBS, serum insulin levels and HOMA-IR [17].

Rebecca L.Wilson assessed the circulating zinc level and dietary zinc intake during pregnancy and the associations with pregnancy complications. in this study found that, circulating zinc levels were not different for the pregnancy outcomes[18].

Meta analysis of prospective cohort studies on magnesium intake and risk of diabetes was done by Jia -Yi Dong provides that magnesium intake is significantly inversely associated with type 2 diabetes [4].

J De Haene found that fasting and postprandial zinc concentrations were higher in gdm group compared to IGT group. post prandial zinc concentrations tended to decline in the third trimester in all groups (NGT, IGT, GDM) but only the fall in the IGT group was significant [19].

S.Behboudi-Gandevani in his study he found that there was no statistical significant difference in zinc level and nutritional intake in early pregnancy with gestational diabetes [20].

Z Asemil did a study on magnesium supplementation and metabolic staus in gestational diabetics. he found that magnesium supplementation among women with GDM had beneficial effect on metabolic status and pregnancy outcome [21].

H .Z. Hamdan found no significant correlation between zinc and selenium and gestaional diabetes in his study [22].

Zinc supplementation among GDM women had beneficial effect on metabolic profiles- observed by Maryam Karamali in their study [23].

A study was done by M.Behrashi. this study showed that zn supplementation in gestational diabetes could reduce insulin needs and improve glycemic control and it may also reduce macrosomia incident rates [24].

A study was done by TG Kazi, results of this study showed that mean values of zn, mn, cr were significantly reduced in blood and scalp

hair samples of diabetic patients as compared to control subjects of both genders. The urinary level of these elements were found to be higher in the diabetes patients than in the age matched healthy controls [25].

Giuseppe paolisso, Mario barbagallo studied the role of intra cellular magnesium in insulin resistance. They noticed plasma magnesium levels were inversely correlated with metabolic control and these data suggest that insulin is an important modulator of intracellular magnesium control [26].

A study done in chinese northeast population showed that serum magnesium levels with IGT, IFG, T2D, T1D are significantly lower than that of healthy control. The increased secretion of urinary magnesium was only found in T2D and T1D patients as compared to control [27].

Patrick M. Catalano, John P. Kirwan found that serum magnesium levels were lower in women with type 1 diabetes compared with control women. A reduction in serum magnesium may reflect depressed tissue magnesium levels. Lower lewel of straited muscle magnesium were measured in patients with diabetes requiring insulin [28].

Gestational diabetes women had significantly lower intracellular free magnesium values compared with nonpregnant and normal pregnant individuals in M Bardicef study. These results support the presence of

magnesium depletion in pregnancy itself and to a greater extenet in gestational diabetes [29].

In the third trimester the level of ionized magnesium was statistically significantly elevated in patients with gestational diabetes compared to controls, it was noted by P Ertbeg in their study [30].

In study of MR Nabouli the serum magnesium concentration in gestational diabetes mellitus women was lower that of normal pregnant women but the difference was not significant [31].

Serum level and Rbc magnesium in gestational diabetic women was less than non-diabetic pregnant women in Z A Bouzari study. Results of the study demonstrated that magnesium could be an effective and an underlying factor in identification of disrupted glucose metabolism in pregnant women [32].

F A Mishu evaluated the serum magnesium level in bangladeshi women. The magnesium level was significantly low in second and third trimesters in gdm cases compared to control group [33].

E Mostafavi, A A Nargesi , showed that abdominally obese patients with lower plasma magnesium are more likely to show abnormal OGTT results [34].

A study was done by M P Genova and their team on zinc level. The survey did not identify statistically significant difference between healthy pregnant women and those with GDM in the level of plasma and hemolysate zinc. Both pregnant groups had higher level of intracellular erythrocyte zinc in comparison to non-pregnant individuals [35] .

A Study was done by WB Kinlaw and team on twenty patients with type 2 diabetes mellitus and found that significant depressed serum concentration and hyperzincuria [36].

Antibody against zinc transporter have been detected in type 1 diabetes mellitus patients in the study done by J Jansen and their team [37].

A study done by J Rungby demonstrated that beta cell specific knockout of Znt8 causes glucose intolerance and it affects the insulin secretion [38].

Scott and Fischer first recognized the relationship between zinc and insulin. They found that normal human pancrease contained significant quantities of zinc and the diabetes pancrease contains very little [39].

U G Tasdemir and his colleaques done a study in pregnant women with gestational diabetes. They found that ionized and total magnesium levels were lowered in GDM group as compared with women with normal OGTT [40].

Farzana Akonjeemishu, MA Muttalib showed that serum magnesium level was significantly lower ($p < 0.001$) in second and third trimesters in GDM cases [7].

Diabetic males and females both had significantly ($p<0.01$) increased zinc excretory rates compared with normal males and females. Urinary zinc excretory rate correlated positively with the degree of glycosuria in the study done by PMC Nair and their team [41].

M Murakami et al examined the relationship between insulin secretion and intracellular free mg^{2+} in a rat insulinomacell using a fluorescent dye [42].

C H Sales, L F C Pedrosa have proven that hypomagnesemia has been associated with diabetes mellitus in their study [43].

Magnesium can be used for prognostic assessment in diabetic individuals. It was strongly supported by the study done by V K Srivastava

and their team. In their study hyperglycemia was inversely related to hypomagnesemia and its restoration towards normal by insulin restored the magnesium concentration too and also the magnesium correlated with major diabetic complication [44].

F Mimouni and their team showed that decreased magnesium status may contribute to the high spontaneous abortion and malformation rate in insulin dependent diabetic pregnant women [45].

R K Campbell and their team showed that although lower intracellular magnesium levels is often reflected by hypomagnesemia (lower serum concentration), deficiency often exists even with normal serum levels of magnesium [46].

A Study was done by E R Arqilla and their team. The study includes invivo experiments involved pretreating mice with zinc or sodium followed by i.p iodoinsulin injection and found that liver plasma membrane isolated from mice pretreated with zinc, bound more iodoinsulin than mice pretreated with sodium. Ii demonstrated that added zinc increased the binding and inhibited the degradation of insulin [47].

An experimental study on the effect of zinc nutrition on insulin metabolism was done by H P Roth and M Kirchgessner. In this study zinc deficient rats had unaltered proinsulin contents but they showed a diminished glucose tolerance, lowered serum insulin and an elevated insulin like activity [48].

Zinc supplementation for type 2 diabetics has beneficial effect in elevating their serum zinc level and in improving their glycemic control. Patients supplemented with oral zinc sulfate 30 mg of elemental zinc/day for 3 months. This study was done by R A Al-maroof and S S Al-sharbatti [49].

A study was done by J J Cunningham and R Glenn Brown. They found that zincuria increased by a similar amount in both groups (IDDM AND Non Diabetic) during zinc supplementation with 50 mg of oral zinc for 28 days. These data suggested a potential for toxicity from large dose zinc supplementation [50].

A study was done by J Quarterman, W R Humphries. They found reduced insulin secretion and reduced glucose tolerance in zinc deficient rats [51].

Insulin like effect of ionic zinc were studied in isolated rat adipose tissue. J M May and C S Contoreggi found that the insulin like effects of zinc in adipocytes are not only caused by direct effect on intracellular metabolism, also by indirect effect related to H_2O_2 generation [52].

When deficiency of magnesium is detected its bio organic salts with high bioavailability are indicated as prevention of gestational diabetes mellitus [53].

A J Lostroh, and Krahl M E showed in their study that insulin stimulation of magnesium accumulation is dependent on an actively functioning Na^+ / K^+ ATPase system [54].

Insulin and glucose are important regulator of magnesium metabolism. Intracellular magnesium plays a key role in regulating insulin action, insulin mediated glucose uptake [55].

M Rodriquez, F G Romero were done a double blind placebo control trial in diabetic subjects with decreased serum magnesium levels. Oral supplementation with magnesiumchloride solution restores the serum magnesium levels and improving insulin sensitivity in diabetic subjects received 50 ml $mgcl_2$ orally for 16 weeks than diabetic subjects received placebo [56].

Maternal plasma concentration of zinc, magnesium was estimated by Borella P and their team. They found significant decrease in magnesium in pregnant women with diabetes but increase in plasma zinc was observed. This is probably as a result of reduced zinc uptake by the fetus [57].

Serum zinc concentration in the first trimester of human pregnancy were evaluated in 106 pregnant women. No difference was found in serum zinc level between diabetics and non diabetic subjects in the study done by Breskin et al [58].

Prenatal iron supplementation may adversely affect maternal zinc status. This was observed by Hambidge K M and team. In their study prenatal iron supplementation was negatively correlated with alkaline phosphatase activity and plasma zinc in second and third trimester [59].

Lie J and their team done a study in chinese pregnant women. They observed the concentration of calcium, copper, magnesium were altered during all the trimesters of pregnancy and zinc levels are altered during mid and late pregnancy and postpartum [60].

Zinc ions enhances proinsulin solubility and also play an important role in microcrystalline character of the precipitated insulin granule [61].

P Delva and team studied the interact of the effect of insulin and glucose on intracellular ionized magnesium in human lymphocyte. Magnesium was measured using a fluorimetric method. Insulin capable of increasing intracellular magnesium by modulating the activity of Na / Mg transport system [62].

The american diabetes association has published a statement suggesting that patients who have documented hypomagnesemia and diabetes mellitus receive magnesium supplementation based on the study done by J R White, R K Campell [63].

R Lopez Riraura et al done a study in 85060 women and 42872 men who had no history of diabetes. Magnesium intake was evaluated using a validated food frequency questionnaire every 2-4 years and found the significant inverse association between magnesium intake and diabetes risk [64].

Hypomagnesemia has been linked both to the acute metabolic and late chronic complication of diabetes [65].

In a study done by A H Zargar et al found that zinc and magnesium levels are not altered in NonInsulin Dependent Diabetes Mellitus (NIDDM) [66].

A review was done by L M Dalton and their team on magnesium in pregnancy. This study provides recommend for further study using measurement of red cell magnesium level to know the magnesium status rather than serum magnesium level. Though serum magnesium is the most widely used method but it has significant limitations [67].

MATERIALS AND METHODS

METHODOLOGY

Study design: Cross sectional study

Study place: Department of Obstetrics & Gynecology, Coimbatore Medical College & Hospital, Coimbatore.

Study period: July 2016 to June 2017.

Study subjects: A total of sixty pregnant women with primigravida in the age group of 20 - 35 years were selected for my study from the department of Obstetrics & Gynecology (O & G) after getting their consent. Thirty pregnant women who diagnosed having Gestational Diabetes Mellitus (GDM) by 75 gm OGTT (Oral Glucose Tolerance Test), with the blood sugar level of $\geq$ 140 mg / dl after 2 hours of oral glucose were considered as GDM group (cases), and control group comprised of 30 primi normal pregnant women without gestational diabetes mellitus.

Inclusion Criteria:

- 30 primi pregnant women diagnosed having GDM who were age as well as BMI matched.
- 30 normal primi pregnant women who were also age and BMI matched.
- Pregnant women having antenatal records with height / weight at first booking visit were included.

- Pregnant women were evaluated for the concentration of Zinc (Zn) and Magnesium (Mg) in the serum during 24 to 28 weeks of gestational age.

EXCLUSION CRITERIA:

- Multiple pregnancy
- Abnormal pregnancy
- Obesity (BMI > 30Kg/m^2)
- PCOD
- Pre gestational diabetes
- Elderly primi (Age > 35 years)
- Primi with medical disorders like Hypertension, Diabetes, Heart disease, Liver and Renal disorder, Epilepsy, Skin diseases and Drug intake.

MATERIALS:

Proforma - To obtain a detailed history and clinical examination findings.

Auto analyser - To analysis blood sugar level.

Photometry - To measure serum magnesium , zinc concentration.

METHODOLOGY:

After obtaining clearance from institutional ethical committee, subjects were selected from the outpatient clinic in the department of obstetrics &

gynecology to my study. Subjects were explained about the procedure in detail and informed consent was obtained. A total of sixty pregnant women of primi gravida were selected in the age group of 20 to 35 years. All the subjects were underwent GDM screening with 75 gram oral glucose tolerance test in the second trimester. After their results, subject with blood glucose level of $\geq$ 140 mg / dl were selected as cases (GDM group) and subject with blood glucose level of < 140 mg / dl were considered as control group.

HISTORY TAKING & CLINICAL EXAMINATION:

Detailed history was elicited from the cases and controls to rule out signs and symptoms of pregestational diabetes, cardio vascular, renal, liver diseases and intake of any drugs. Last menstrual period (LMP) was noted, and weeks of pregnancy was calculated using Naegele's rule (Add 7 days to the first day of LMP and count back 3 months). General examination was done.

HISTORY TAKING

BMI (Body Mass Index) MEASUREMENT:

The height as well as weight recorded during the first visit of antenatal checkup were obtained from the antenatal records and BMI was calculated using Quetelet's index.

QUETELET'S INDEX:

Body Mass Index (BMI) = Weight in kg / Height in m^2

The subjects were selected with a BMI between 18.5 to 24.99 kg/m^2 which includes women with normal BMI according to WHO (World Health Organization) criteria.

BLOOD INVESTIGATION: (Done in all subjects)

1. **TWO HOUR 75 gm OGTT -** (WHO CRITERIA)

The test was done at 24 to 28 weeks of pregnancy. it was done irrespective of the last meal. It is a screening test for gestational diabetes mellitus.

All the pregnant women were given a 75 gm glucose load orally in the antenatal clinic, then a blood sample was collected from a peripheral vein after 2 hours and the estimation of plasma glucose was done using glucose oxidase peroxidase technique.

ORAL GLUCOSE TOLERANCE TEST

OGTT RESULTS:

Blood glucose level of ≥ 140 mg / dl - Abnormal. Subjects with this value taken as cases.

Blood glucose level of < 140 mg / dl - Normal. Subjects with this value taken as controls.

SERUM ZINC & MAGNESIUM MEASUREMENT:

It was done in both groups of subjects (case & control).

In all subjects the antecubital vein in front of forearm was selected for venous blood sample. The skin over the vein was cleaned with spirit & cotton and allowed to dry. Then a disposable sterile needle fitted with 5 ml syringe was introduced and 4 ml of blood was collected and poured into separate container. The serum was separated from this sample by centrifuging the blood to 3000 rpm for five minutes. And the serum was used to estimate the serum zing and magnesium levels immediately.

ZINC ; NITRO - PAPS METHOD : (CALORIMETRIC METHOD)

The estimation of serum zinc was done using NITRO - PAPS method.

PRINCIPLE:

Zinc reacts with Nitro - PAPS reagent in alkaline medium to form a purple coloured complex.

NORMAL VALUE: 70 - 115 µg / dl.

VENOUS BLOOD SAMPLE COLLECTED FOR ZINC AND MAGNESIUM MEASUREMENT

MAGNESIUM : MODIFIED XYLIDYL BLUE REACTION METHOD:

The estimation of serum magnesium was done using Modified xylidyl blue reaction method.

PRINCIPLE:

Magnesium determination is based on the reaction of magnesium with xylidyl blue at alkaline pH, which yields a purple coloured complex.

NORMAL VALUE : 1.30 - 2.70 mg / dl.

NORMAL VALUES OF ZINC, MAGNESIUM AND OGTT:

Parameters	Normal Values
OGTT	In Pregnancy: < 140 mg / dl (Normal) ≥ 140mg/dl (GDM)
Zinc	70 – 115 µg / dl
Magnesium	1.30 – 2.70 mg / dl

STATISTICAL ANALYSIS

STATISTICAL TOOLS

The data obtained from the current study were documented in a Master Chart. Data Analysis was done using statistical packaging of social science – SPSS Version 24.

Employing the above software calculations of the mean, standard deviations (SD), percentages and ‘p’ values were done. Student ‘t’ test was employed to analyse the significance of difference between the quantitative variables (age, BMI, Zinc, Magnesium, OGTT). Chi square test is used for qualitative variables (diet, residence, family history). A significant association is considered only when the ‘p’ value is less than 0.05.

Microsoft power point was employed to prepare graphs.

RESULTS

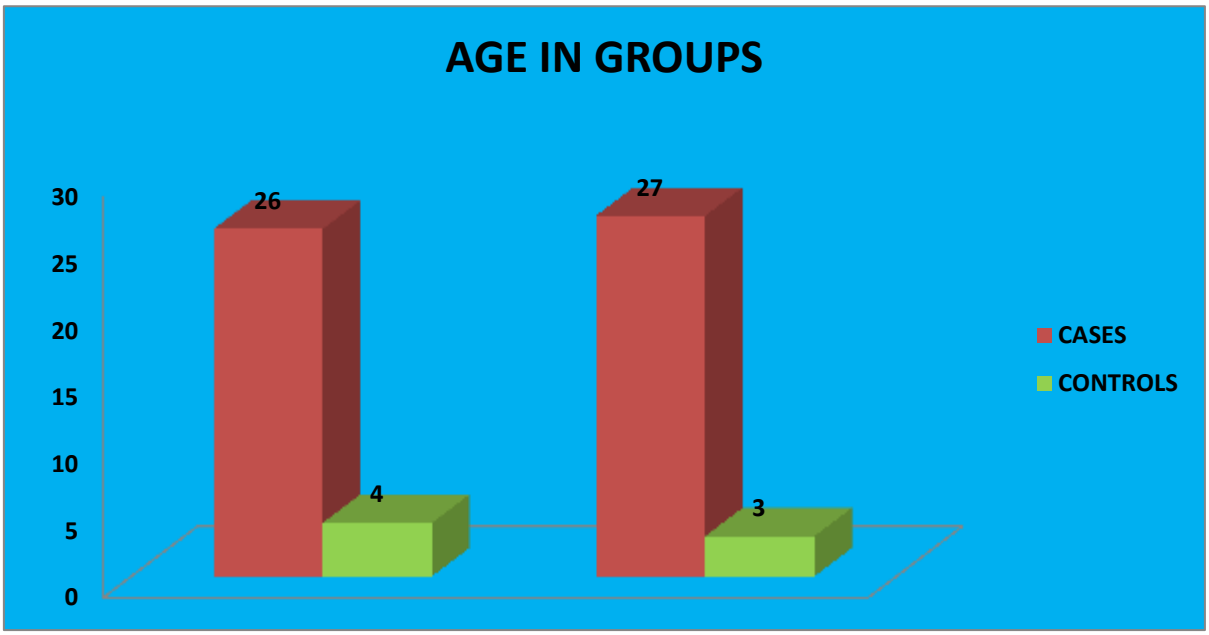
RESULTS

Table 1: AGE DISTRIBUTION BETWEEN THE GDM GROUP AND THE CONTROL GROUP.

Age	Case (GDM)	Control	P value
20-25	26(49.1%)	27(50.9%)	0.688
26-30	4(57.1%)	3(42.9%)	

p- value > 0.05 - not statistically significant.

Figure : 1 AGE DISTRIBUTION



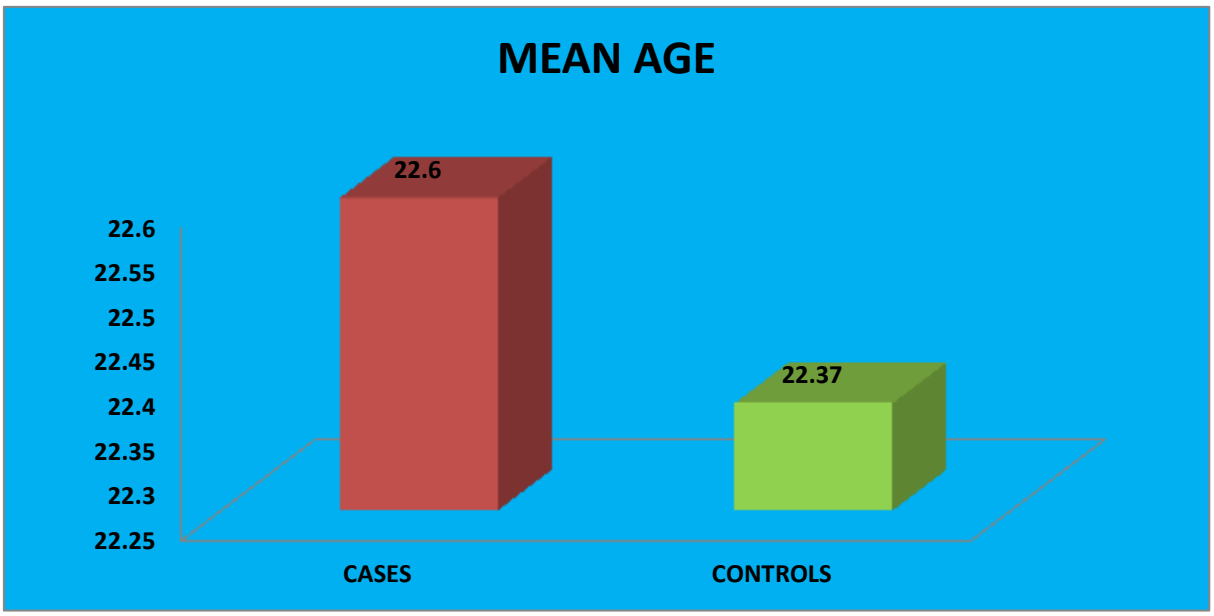
In this study there is no statistically significant difference in age distribution between GDM group and control group.

Table 2: MEAN AGE

	GROUPS	N	Mean	Standard Deviation(SD)	Range	'P' VALUE
Age	Case	30	22.60	2.358	20-29	0.687
	Control	30	22.37	2.092	20-27	

Not statistically significant ($p > 0.05$)

Figure : 2 MEAN AGE



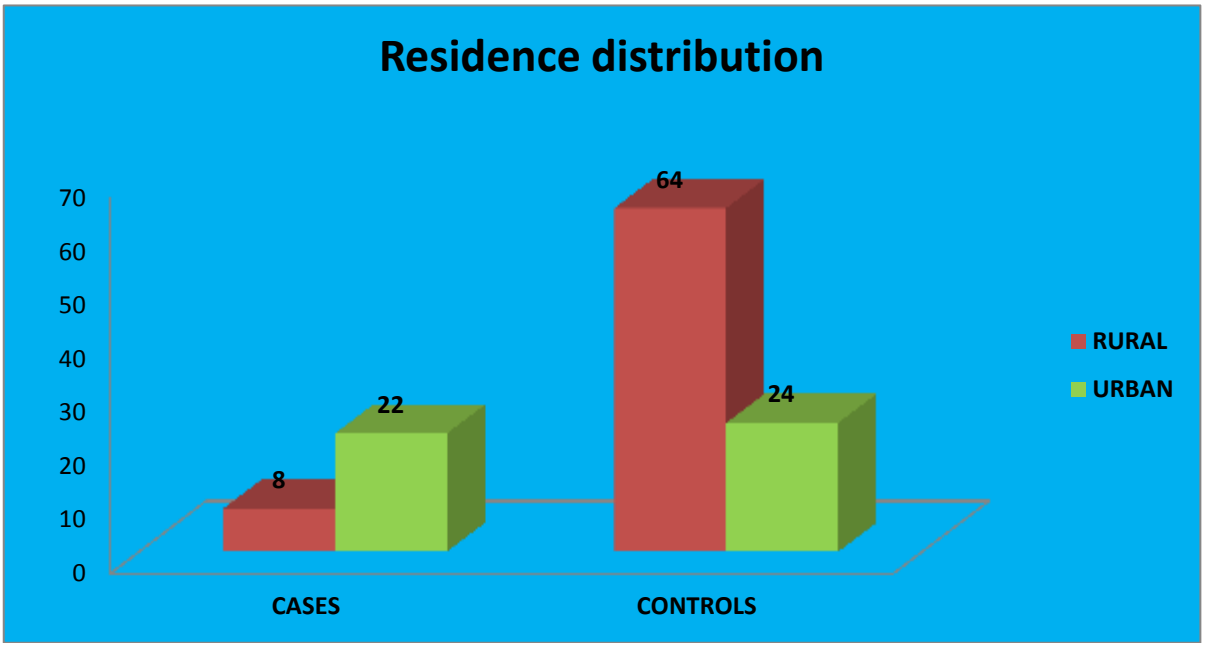
There is no statistically significant difference in age distribution between GDM group and control group.

Table 3 : DISTRIBUTION OF RESIDENCE BETWEEN GDM GROUP AND CONTROL GROUP

Residence	Case (GDM) group	Control group	'P' value
Rural	8(57.1%)	6(42.9%)	0.542
Urban	22(47.8%)	24(52.2%)	

p -value : 0.542 (> 0.05), Not significant.

Figure : 3 RESIDENCE



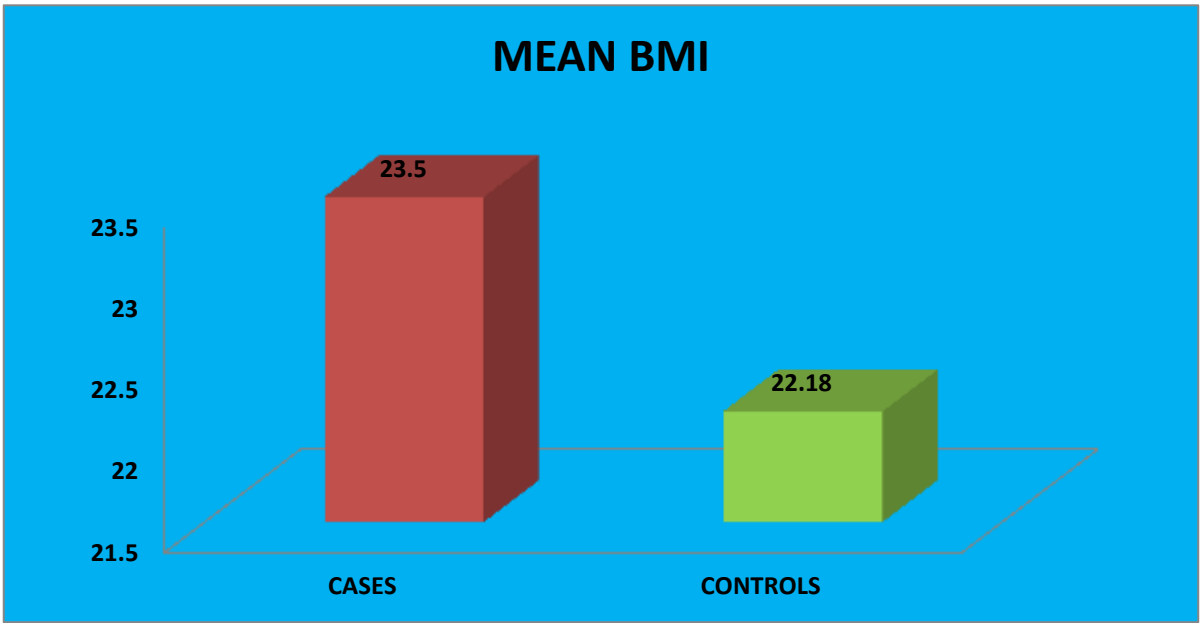
There is no significant difference in residence distribution between GDM group and control group.

Table 4 : BMI DISTRIBUTION BETWEEN GDM GROUP AND CONTROL GROUP

	GROUPS	No	Mean	Standard Deviation(SD)	'P' value
BMI	**Case**	30	23.50	1.7	0.002*
	Control	30	22.18	1.4	

*- STATISTICALLY SIGNIFICANT (P<0.05)

Figure : 4 MEAN BMI



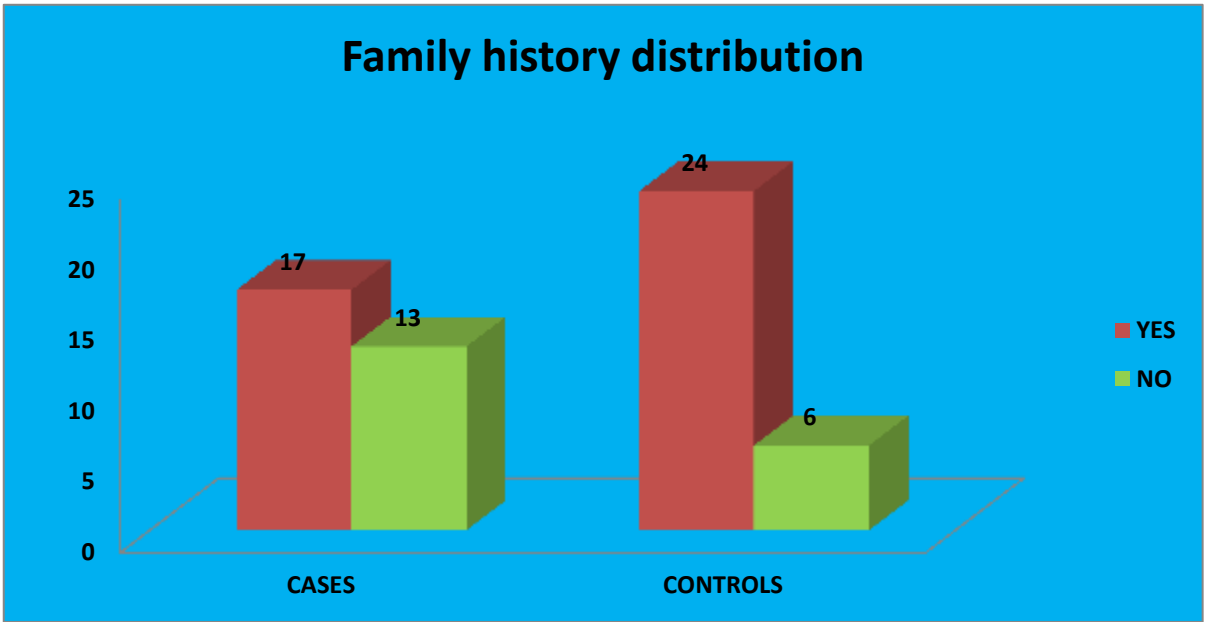
The above results show significant difference in BMI distribution between GDM group and control group.

Table 5 : FAMILY HISTORY OF DIABETES MELLITUS

Family h/o DM	Case(GDM)	Control	'P' value
Yes	17(41.5%)	24(58.5%)	0.052
No	13(68.4%)	6(31.6%)	

p > 0.05, Not statistically significant.

FIGURE : 5 FAMILY HISTORY OF DIABETES



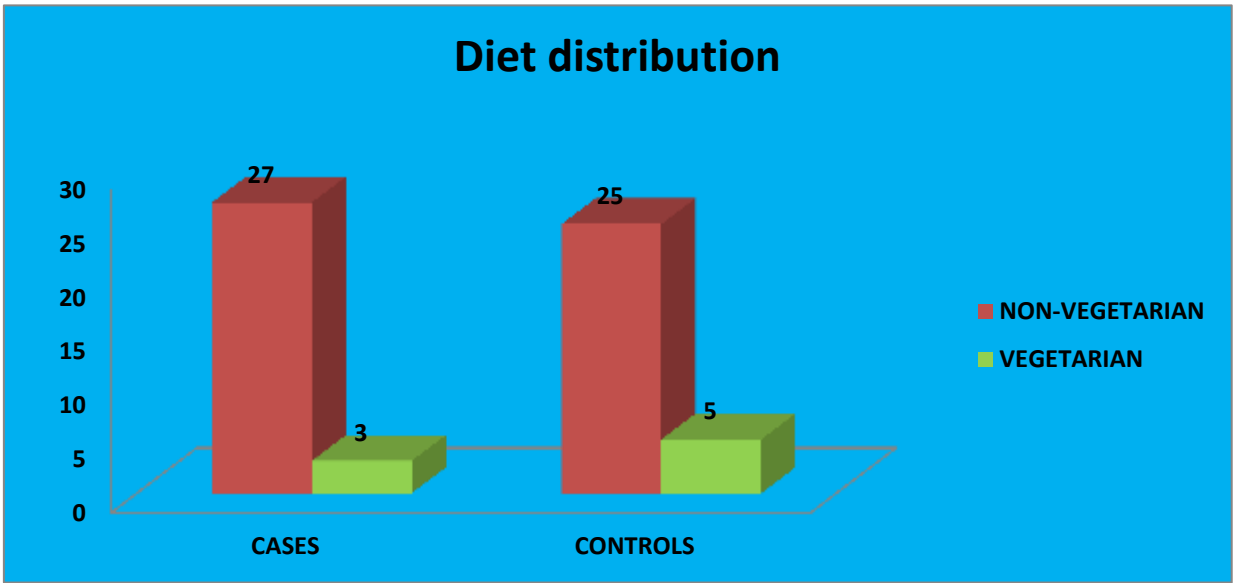
Both groups show no significant difference in distribution of family history of diabetes mellitus.

Table 6 : DIET HABITS BETWEEN GDM GROUP AND CONTROL GROUP

Diet Habit	Case(GDM)	Control	'P' value
Non -vegetarian	27(51.9%)	25(48.1%)	0.448
Vegetarian	3(37.5%)	5(62.5%)	

'p' - value : 0.448 (Not significant).

FIGURE : 6 DIET HABITS



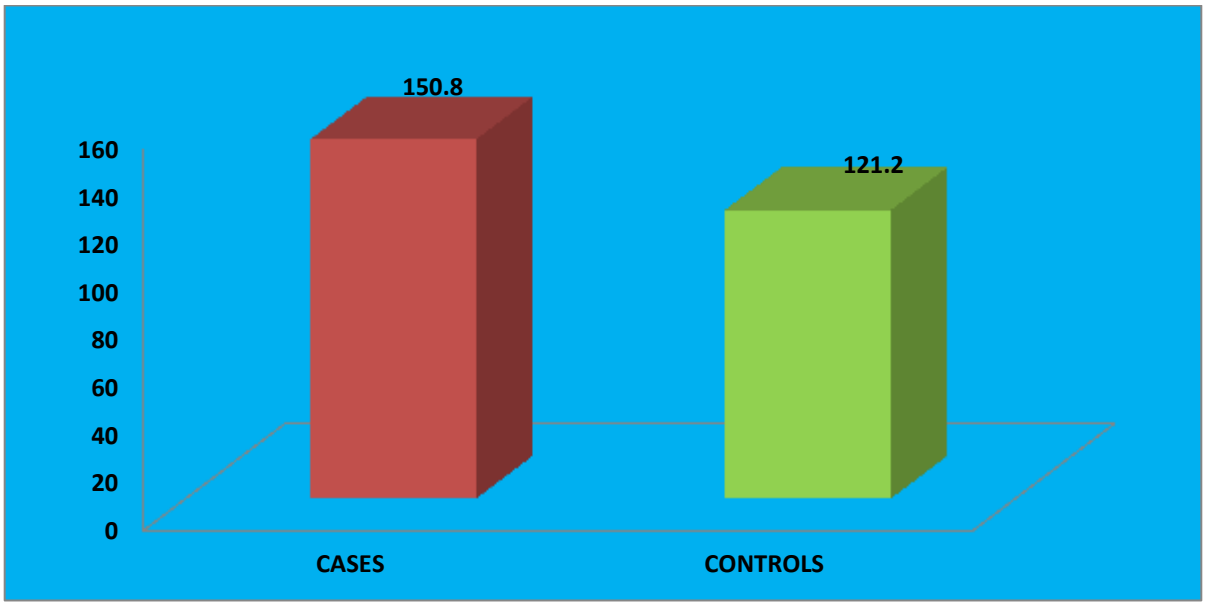
Both groups show no significant difference in the diet habit.

Table 7 : OGTT VALUES BETWEEN GDM AND CONTROL GROUP

	GROUPS	Number	Mean	Standard Deviation(SD)	'P ' value
OGTT	**Case (GDM)**	30	150.80	8.08	.000*
	Control	30	121.20	6.17	

*- STATISTICALLY SIGNIFICANT (P<0.05)

FIGURE : 7 OGTT VALUES BETWEEN GDM GROUP AND CONTROL GROUP



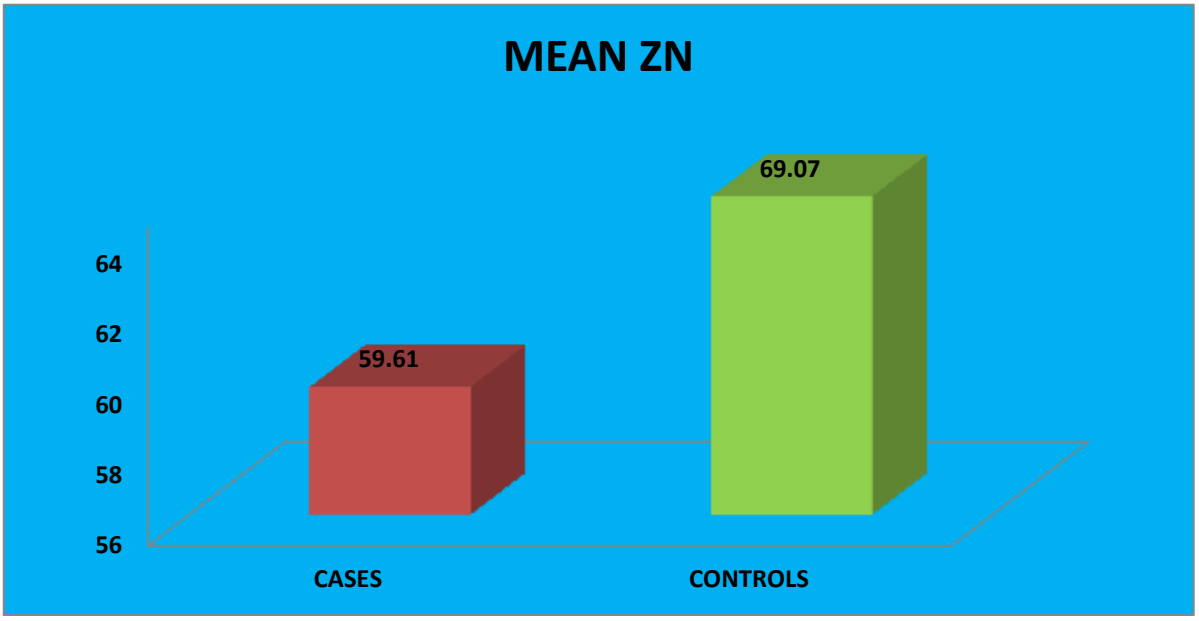
There is statistically significant difference in OGTT values between GDM group and control group.

Table 8 : ZINC LEVELS BETWEEN GDM GROUP AND CONTROL GROUP

	GROUP	N	Mean	Standard Deviation(SD)	'P' VALUE
Zinc	**Case (GDM)**	30	59.61	8.0	.000*
	Control	30	69.07	10.8	

*- STATISTICALLY SIGNIFICANT (P<0.05).

FIGURE : 9 ZINC LEVEL IN GDM GROUP AND CONTROL GROUP



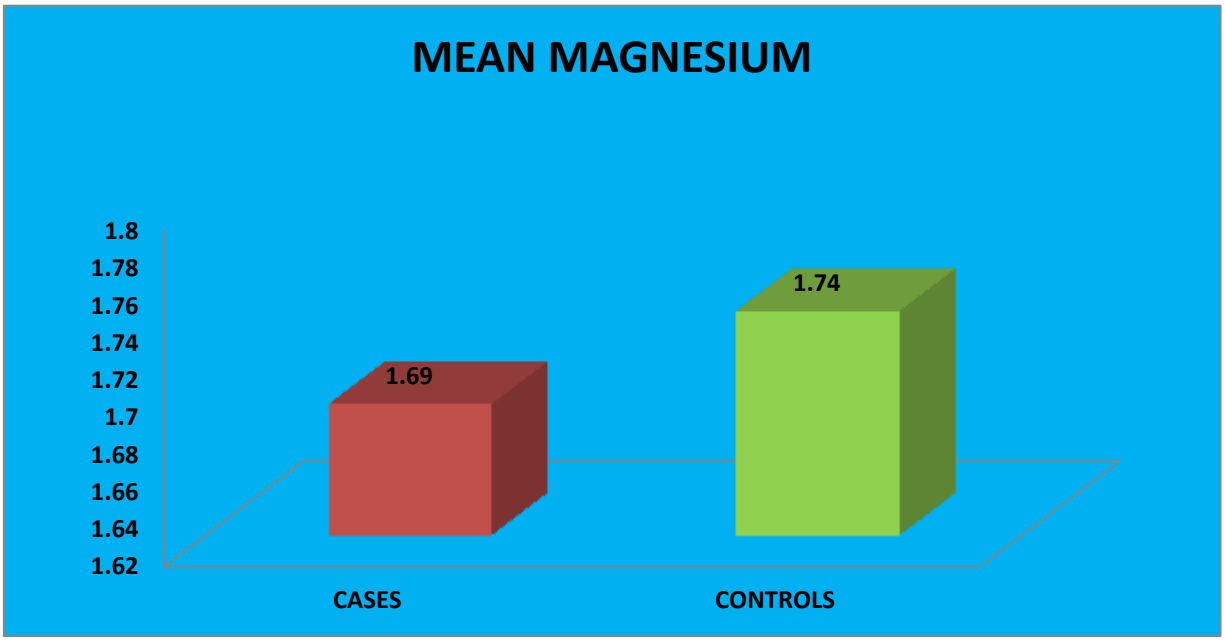
Mean zinc in GDM group was 59.61 µg / dl, and the level of mean zinc in normal primi gravida (control group) was 69.07 µg/ dl. The p- value is 0.000 (<0.05) statistically significant. Zinc level in the GDM group was significantly lower than control group.

Table 9 : MAGNESIUM LEVEL BETWEEN GDM GROUP AND CONTROL GROUP

	GROUP	No	Mean	Standard Deviation(SD)	'P' value
Magnesium	**Case (GDM)**	30	1.69	.33	0.598
	Control	30	1.74	.33	

NOT STATISTICALLY SIGNIFICANT (p - 0.598)

FIGURE : 10 MAGNESIUM LEVEL IN GDM GROUP AND CONTROL GROUP



Mean magnesium in GDM group was 1.69 mg/ dl, and mean magnesium in control group was 1.74 mg / dl. The 'p' value is 0.598. There is no significant difference in magnesium level in both the groups.

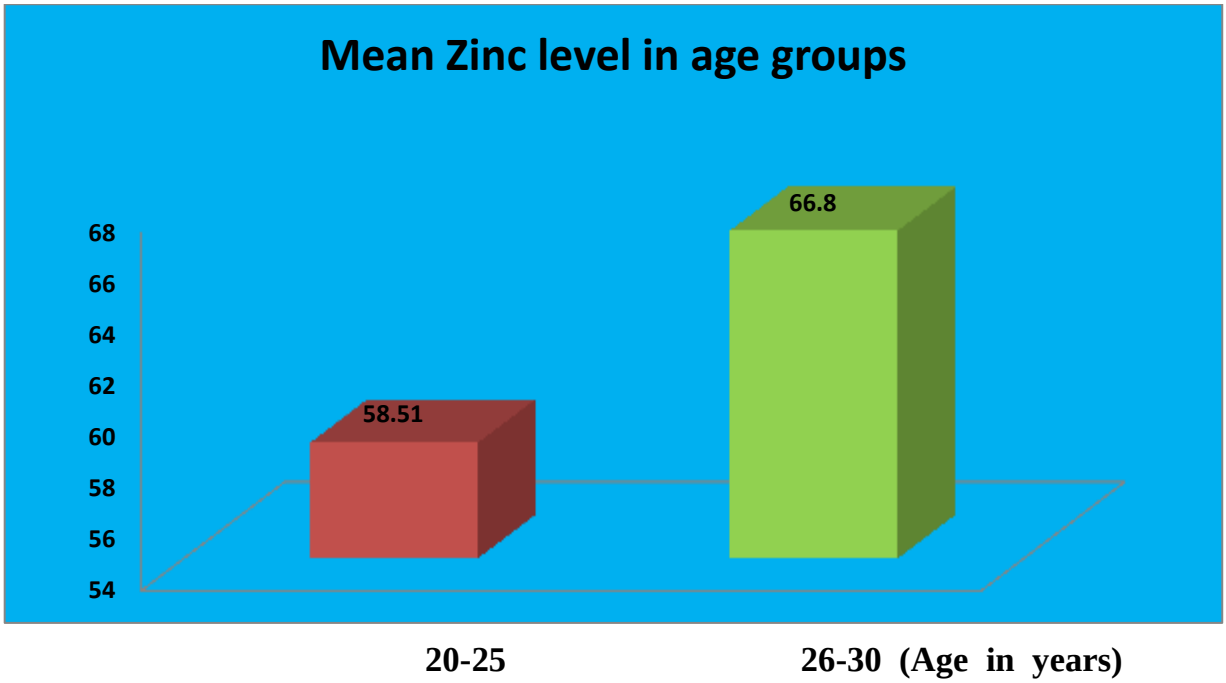
ASSOCIATION BETWEEN ZINC AND OTHER VARIABLES IN GDM GROUP

Table 10 : AGE & ZINC LEVELS

	Age	No	Mean	Standard Deviation(SD)	'P' value
Zinc	20-25	26	58.51	7.1	0.219
	26-30	4	66.80	10.6	

NOT STATISTICALLY SIGNIFICANT (P : 0.219)

FIGURE : 10 AGE & ZINC LEVELS

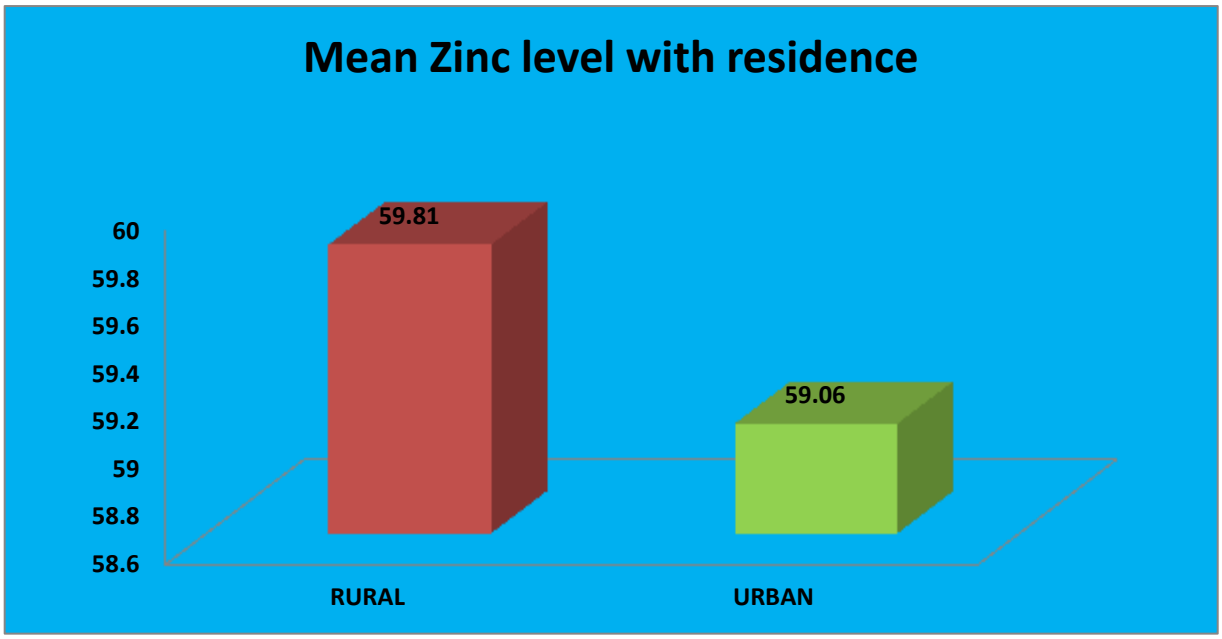


There is no significant relation between age and zinc level in GDM group.

Table 11 : DISTRIBUTION OF RESIDENCE & ZINC LEVELS IN GDM GROUP

	Residence	No	Mean	Standard Deviation(SD)	'P' value
Zinc	Urban	22	59.81	8.6	0.824
	Rural	8	59.06	6.2	

FIGURE : 11 RESIDENCE & ZINC LEVELS



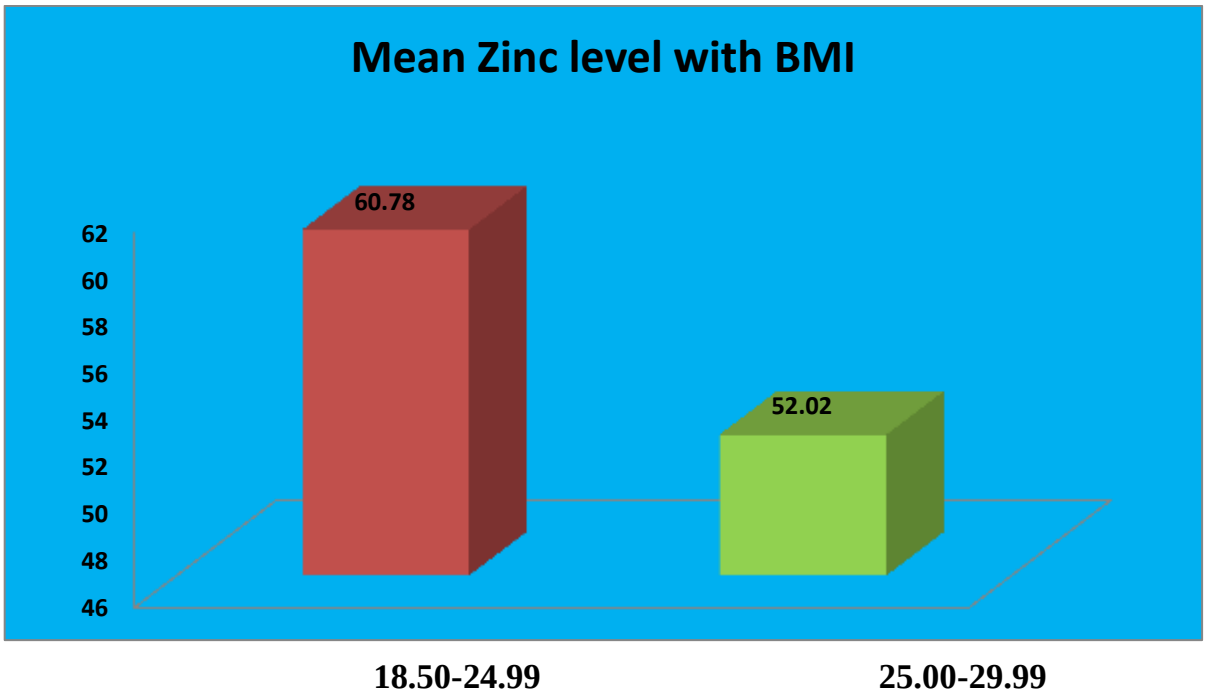
There is no relation between rural & urban residential distribution and zinc level in GDM group.

Table 12 : BMI & ZINC LEVELS

	BMI	No	Mean	Standard Deviation(SD)	'P' value
Zinc	18.50-24.99	26	60.78	7.9	0.039*
	25.00-29.99	4	52.02	1.0	

'p' value 0.039 (< 0.05) ; significant.

FIGURE : 12 BMI & ZINC LEVELS



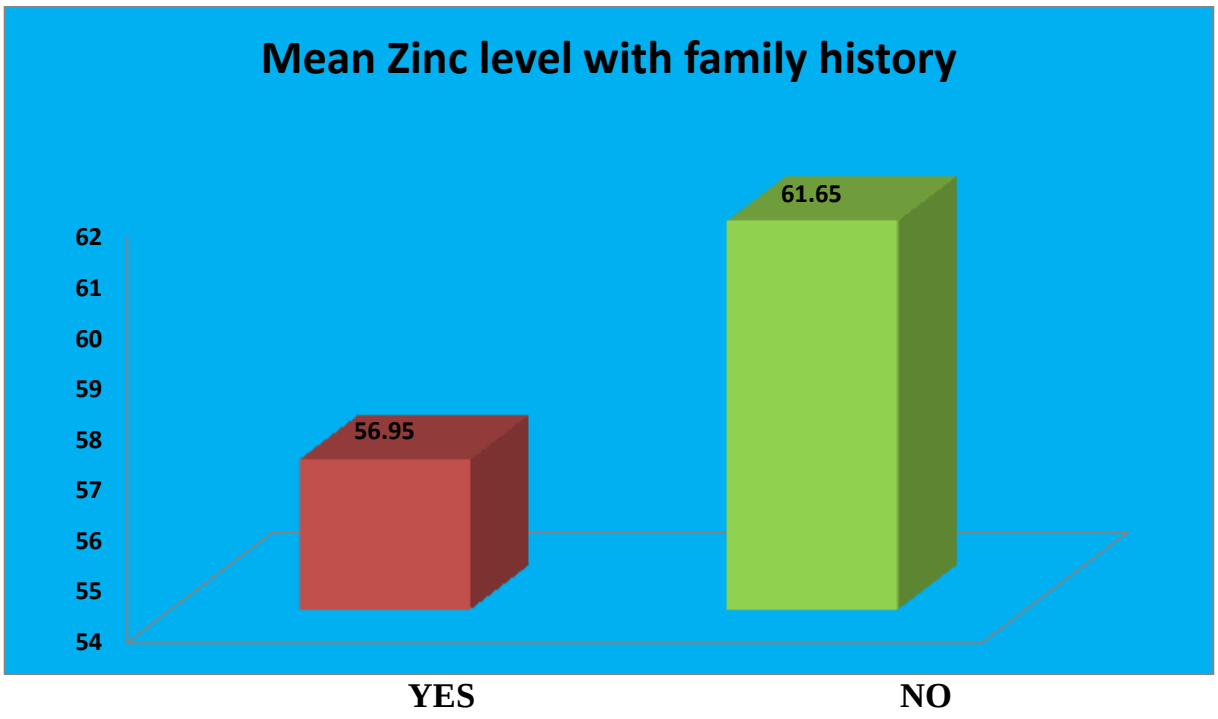
In the GDM group, mean zinc in the subjects with normal BMI was 60.78µg / dl and mean zinc level in overweight GDM group was 52.02 µg / dl. p value was statistically significant. The above results show deficiency of zinc level was increase with overweight .

Table 13 : FAMILY HISTORY OF DM & ZINC LEVELS

	Family history	No	Mean	Standard Deviation(SD)	'P' value
Zinc	YES	13	56.95	6.86	0.113
	NO	17	61.65	8.41	

'p' value 0.113 (>0.05) Not Significant.

FIGURE : 13 FAMILY HISTORY OF DIABETES AND ZINC LEVELS



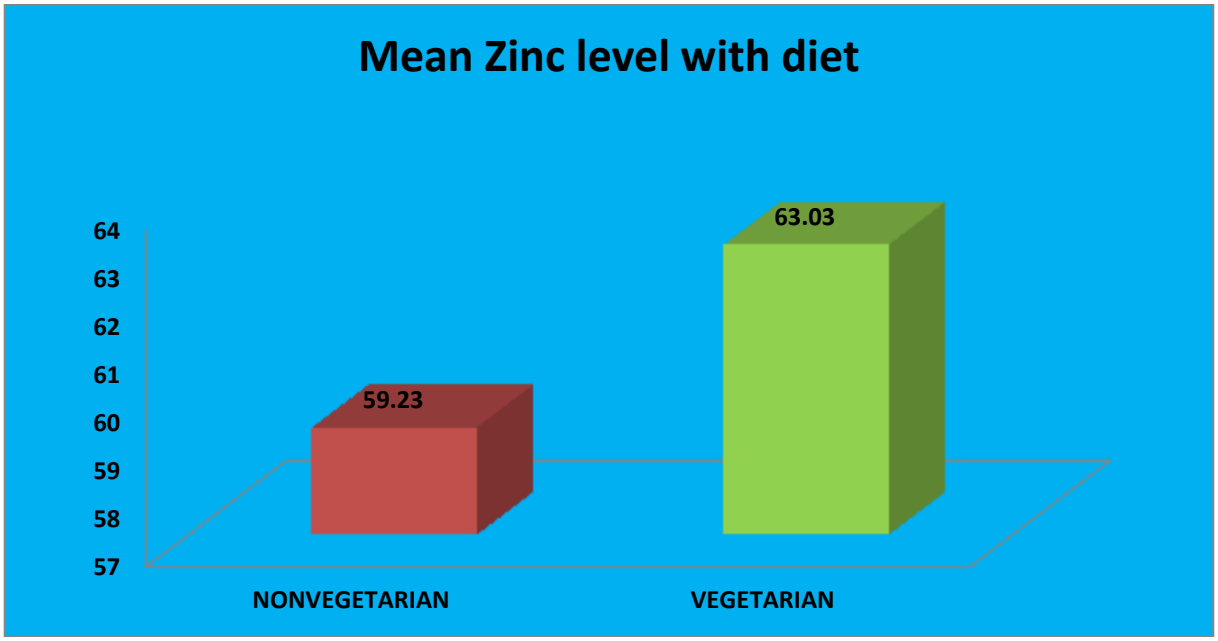
In the GDM group there is no statistically significant difference in zinc level between subjects with positive family history and subjects with no family history of diabetes mellitus

Table 14 : DIET HABIT & ZINC LEVELS IN GDM GROUP

	Diet	No	Mean	Standard Deviation(SD)	'P' value
Zinc	**NON-VEGETARIAN**	27	59.23	7.4	0.446
	VEGETARIAN	3	63.03	13.5	

'p' value- not significant (0.446).

FIGURE : 14 DIET HABIT & ZINC LEVELS



The above results show no significant difference of zinc level between vegetarian and non-vegetarian in GDM group.

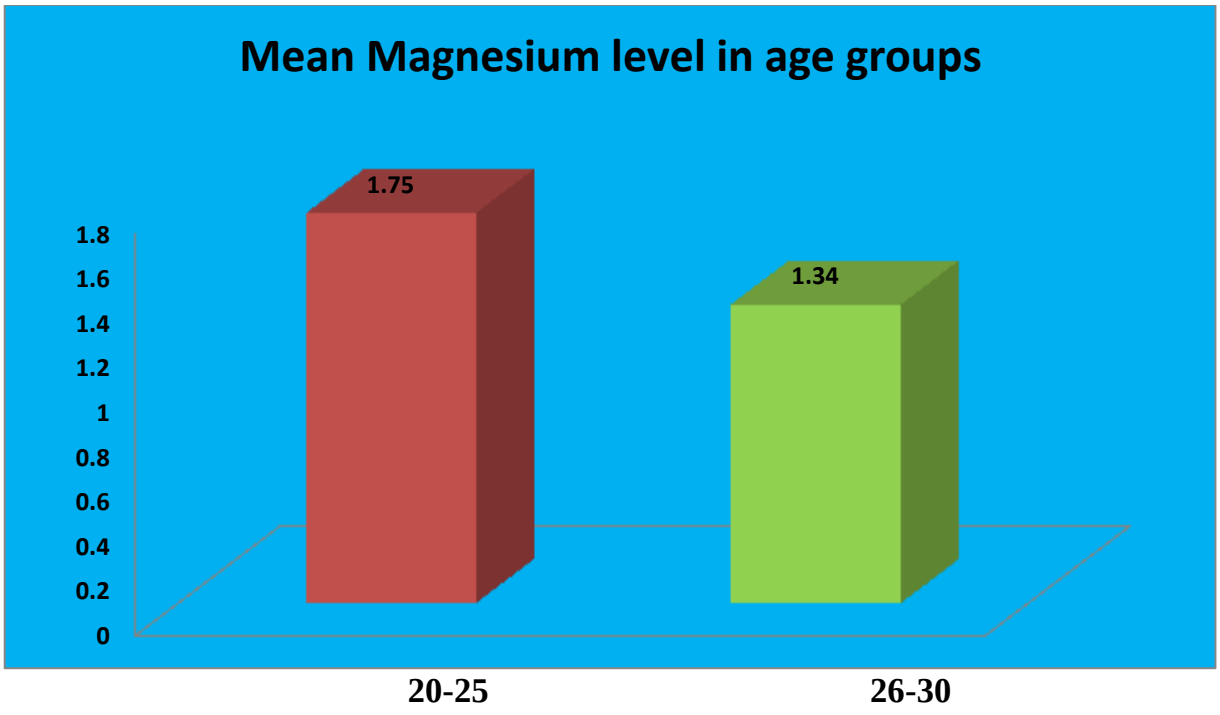
ASSOCIATION BETWEEN MAGNESIUM AND OTHER VARIABLES IN GDM GROUP.

Table 15 : AGE & MAGNESIUM LEVELS

	Age	No	Mean	Standard Deviation(SD)	'P 'value
Magnesium	20-25	26	1.75	.29	0.103
	26-30	4	1.34	.36	

'p' 0.103 ; Not Significant.

FIGURE : 15 AGE & MAGNESIUM LEVELS



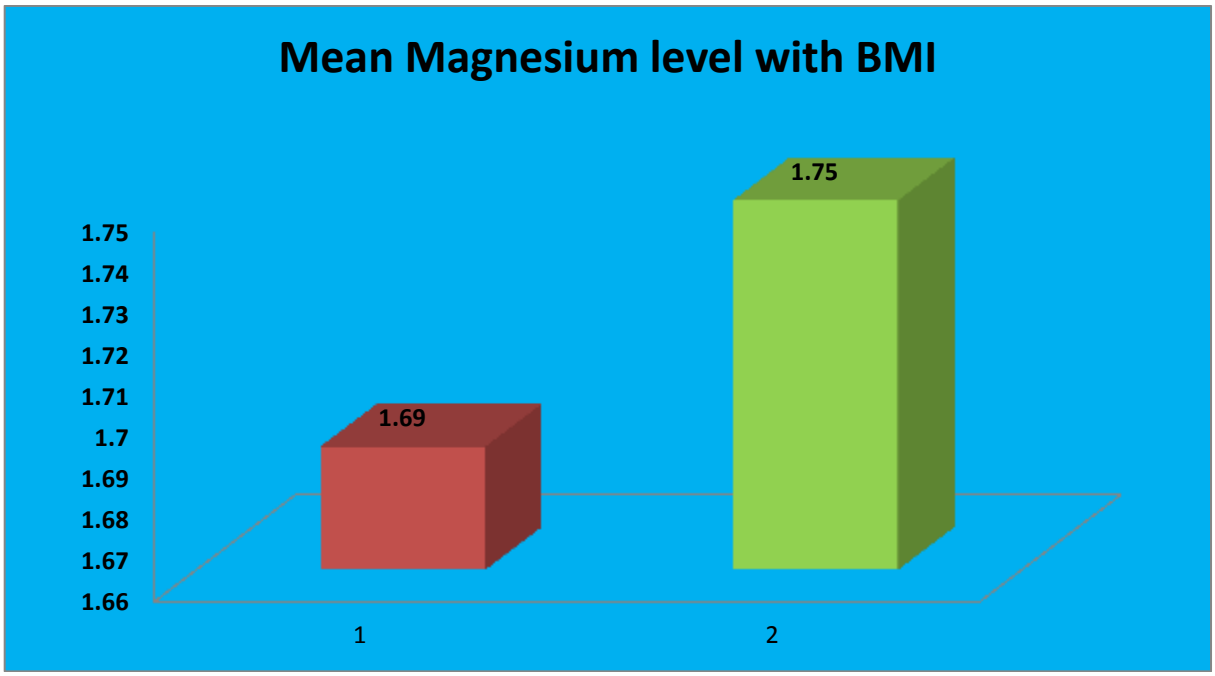
There is no significant relation between age and magnesium level in GDM group.

Table 16 : BMI & MAGNESIUM LEVEL IN GDM GROUP

	BMI	No	Mean	Standard Deviation(SD)	'P' value
Magnesium	18.50-24.99	26	1.69	.34	0.714
	25.00-29.99	4	1.75	.29	

p value : 0.714 (>0.05), Not Significant.

FIGURE : 16 BMI & MAGNESIUM LEVELS



18.50-24.99 **25.00-29.99**

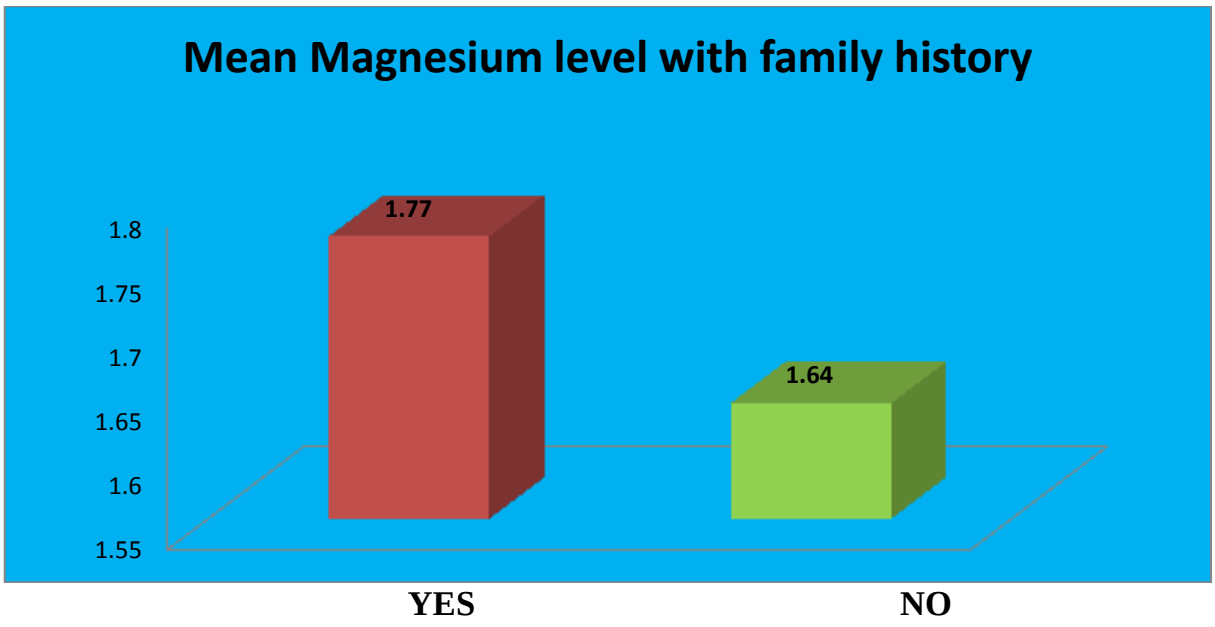
In GDM group mean magnesium of subjects with normal BMI was 1.69 mg / dl, and mean magnesium level in subjects with overweight was 1.75 mg / dl. There is no statistically significant difference between BMI distribution and magnesium level .

Table 17 : FAMILY HISTORY OF DM & MAGNESIUM IN GDM GROUP

	Family history	No	Mean	Standard Deviation(SD)	'P' value
Magnesium	YES	13	1.77	.26	0.276
	NO	17	1.64	.37	

p value 0.276 (> 0.05) Not significant.

FIGURE : 17 FAMILY HISTORY OF DIABETES AND MAGNESIUM LEVELS



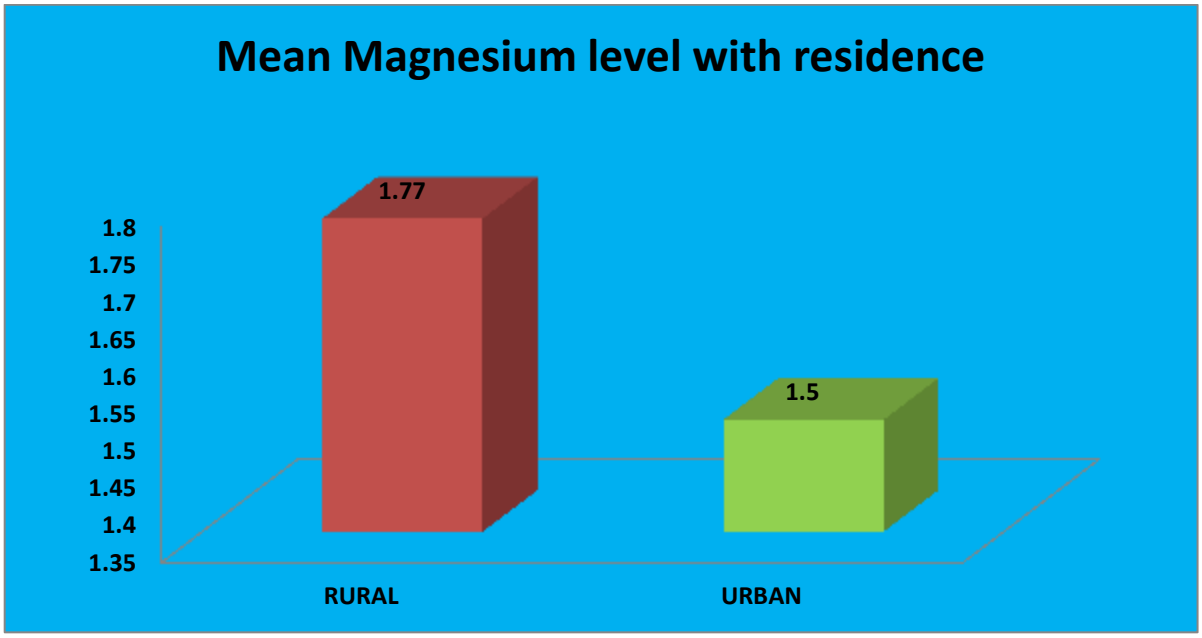
There is no significant relation between family history of diabetes mellitus and magnesium level in GDM group.

Table 18 : RESIDENCE & MAGNESIUM LEVEL IN GDM GROUP

	Residence	No	Mean	Standard Deviation(SD)	'P' value
Magnesium	Urban	22	1.77	.29	0.994
	Rural	8	1.50	.37	

p value ; 0.994 - Not Significant.

FIGURE : 18 RESIDENCE & MAGNESIUM LEVELS



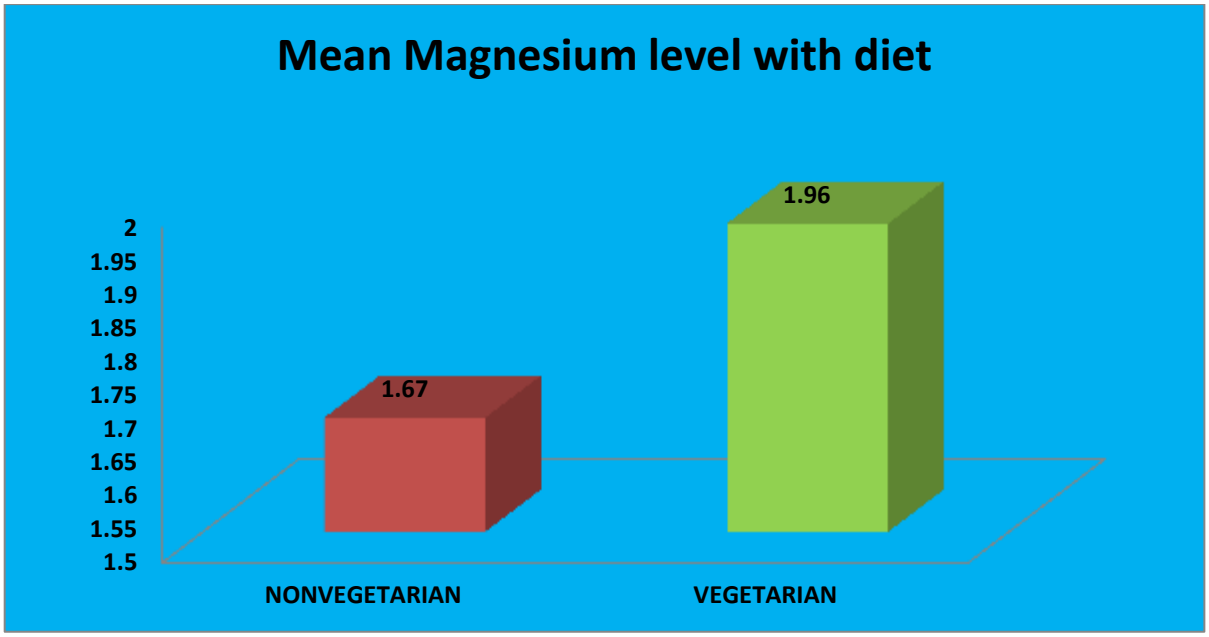
No significant difference in magnesium level between rural and urban residential distribution in GDM group.

Table 19 : DIET HABIT & MAGNESIUM LEVEL

	Diet	No	Mean	Standard Deviation(SD)	'P' value
Magnesium	**NON-VEGETARIAN**	27	1.67	.33	0.151
	VEGETARIAN	3	1.96	.15	

'p' value ; 0.151 (>0.05) : Not Significant.

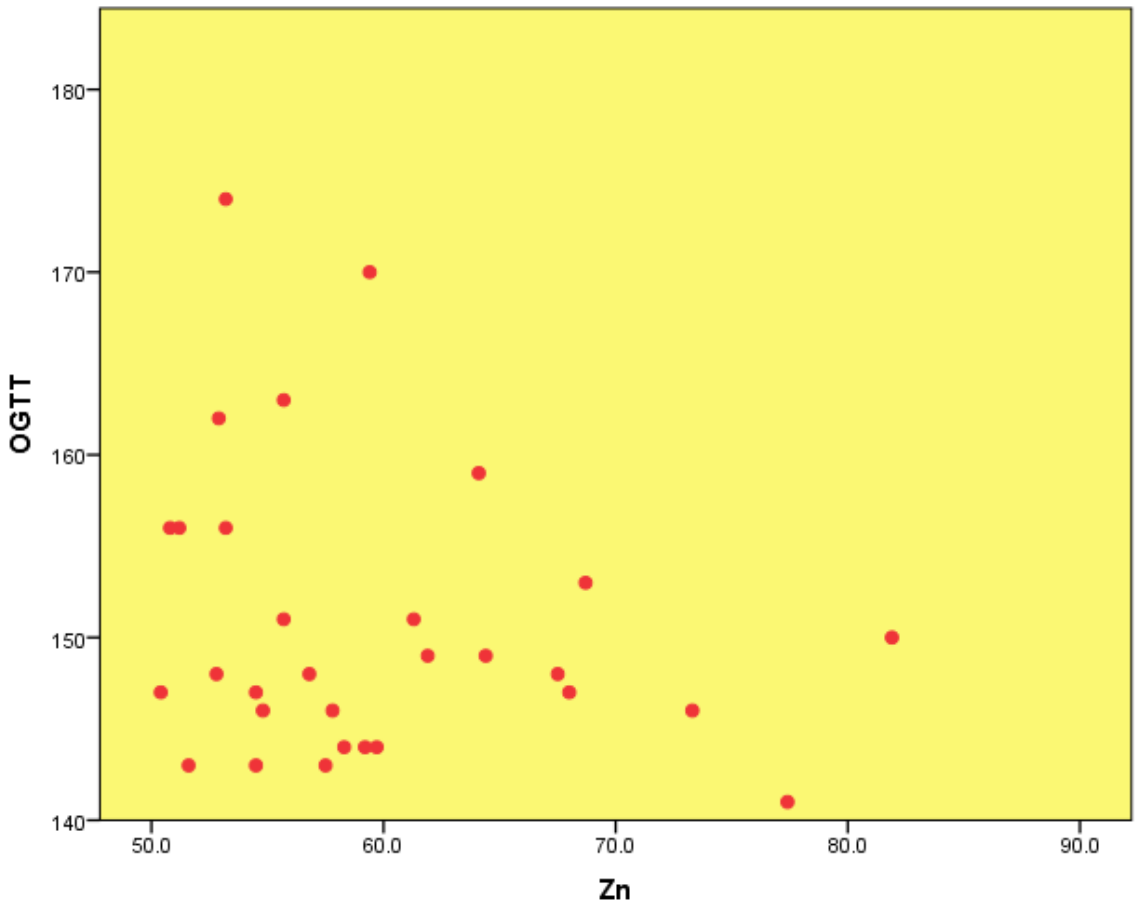
FIGURE : 19 DIET HABIT & MAGNESIUM LEVELS



There is no significant difference in magnesium level between vegetarian and non-vegetarian in GDM group.

Table 20 : CORRELATION BETWEEN OGTT AND ZINC

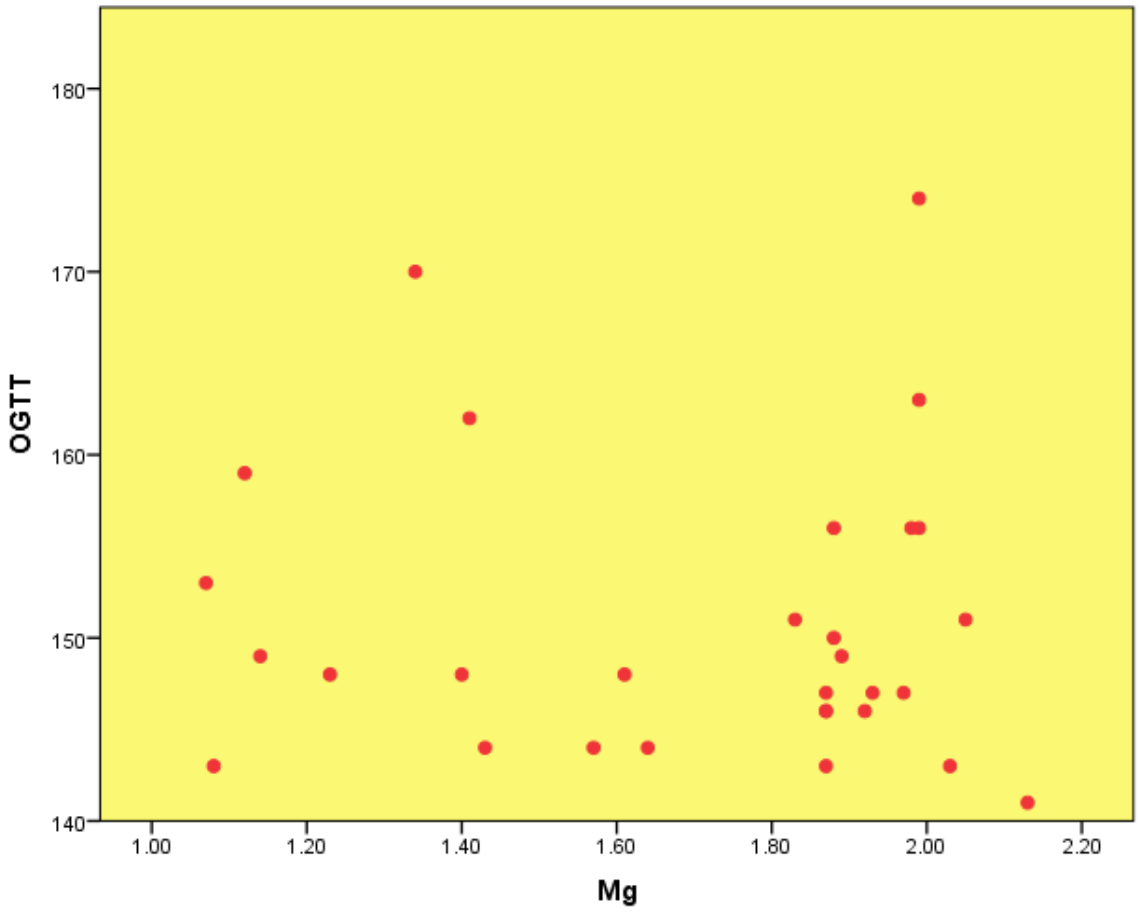
	No	Mean	Standard Deviation(SD)	Correlation	'P' value
OGTT	30	150.80	8.08	- 0.226	0.231
Zinc	30	59.617	8.01		



Correlation coefficient between blood sugar levels by OGTT and zinc is found - 0.226 (negative correlation). This show that as the zinc level decreases the blood sugar level increase in women with GDM.

Table 21 : CORRELATION BETWEEN OGTT AND MAGNESIUM

	N	Mean	Standard Deviation(SD)	Correlation	'P' value
OGTT	30	150.80	8.08	- 0.058	0.113
Magnesium	30	1.69	.33		



Correlation coefficient between blood sugar levels by OGTT and magnesium is found - 0.058 (negative correlation). This shows that as magnesium level decreases the blood sugar level increases in women with GDM.

DISCUSSION

DISCUSSION

Pregnancy is a state of insulin resistance. Many maternal hormones and factors play a role in causation of insulin resistance during pregnancy. Insulin resistance during pregnancy due to alteration in the hormonal level such as growth hormone, cortisol, human placental lactogen and insulinase secretion. In healthy pregnant women insulin resistance is compensated by pancrease, but in gestational diabetes mellitus women there is a impaired beta cell function.

Gestational diabetes mellitus is defined as glucose intolerance that begins or is first recognized during pregnancy. Women without diabetes develops high blood sugar levels during pregnancy. Babies born to mothers with poorly treated gestational diabetes are at increased risk of being too large, having low blood sugar after birth and jaundice. Longterm children are at higher risk of being overweight and developing type 2 diabetes mellitus.

GDM is caused by not enough insulin in the setting of insulin resistance. In a normal pregnancy insulin resistance develop in the second trimester and continues until birth. It is beleived to be related to the production of hormones, cytokines, adipokines by the placenta. Gestational diabetes develops because of preexisting increase insulin resistance and

diminished insulin secretion. During pregnancy the imbalance between insulin resistance and secretion may lead to hyperglycemia.

Women with GDM are often asymptomatic, so screening is important for detection. Screening protocol for GDM is controversial. Screening may consist of either a one step 0approach or a two step approach. The one step approach was initially recommended by the ADA in 2011. It involves a 75g OGTT at 24- 28 weeks gestation. Women who are at risk of preexisting diabetes should be screened at their first prenatal visit. Routine screening of women with a glucose challenge test appears to find more women with gestational diabetes than only screening women with risk factors. A women is considered low risk if age less than 25 years, BMI less than 25 before pregnancy, not of american indian, asian women, hispanic, african american, no first degree relative with diabetes mellitus, no history of poor obstetric outcome. A women is considered high risk if all of the following factors are present history of macrosomia, age > 25 years, BMI > 30, ethnic group with a higher rate of type 2 diabetes, strong family history of diabetes, unexplained stillbirth, persistent glycosuria.

The specific aim of this study was to pursue possible relationships between serum concentration levels of zinc and magnesium micronutrients and gestational diabetes mellitus. GDM is a complex metabolic syndrome and many factors are contributed in this disorder. The causes of gdm are

multifactorial and may include genetic and environmental factors that influence insulin sensitivity.

Zinc is mainly an intracellular element. Zinc is found in many foods. The main sources of zinc are meat, fish, egg, milk, beans, nuts. Zinc is absorbed mainly in duodenum. Zinc is better absorbed from animal foods than from plant foods since phytate hinder its absorption. Zinc is an essential component of several enzymes. How does zinc relate to diabetes? Interestingly zinc has long been an ingredient used in older insulins. Zinc is also necessary for the storage and secretion of insulin from the beta cells of pancrease. Insulin is stored inside secretory vesicles or granules where 2 zinc ions coordinate six insulin monomers to form hexameric structure on which matured insulin crystals are based. Only a small portion of insulin stored in vesicles released even under maximum stimulation, this suggest that insulin synthesis are regulated by secretion rather than synthesis and is not ordinarly limited by size of storage pool. Zinc affects insulin signalling pathway. Zinc potentiates the motogenic signalling of insulin and activates extracellular signal regulated kinases 1 and 2 [5]. Zinc has insulin like function, increase the glucose transport into rat epididymal adipocytes through a post insulin receptor mechanism [68].

Magnesium is the fourth most abundant cation in the body. 70% of which is found in bones in combination with calcium and phosphorous.

The main sources of magnesium are cereals, nuts, beans, cabbage, cauliflower, meat, milk, fruit. Magnesium is absorbed by the intestinal cells through a specific carrier system. About 50% of the dietary magnesium is normally absorbed. Consumption of large amount of calcium, phosphate and alcohol diminishes magnesium absorption. Homeostasis is maintained by intestinal absorption as well as by renal excretion. Magnesium is the activator of many enzymes requiring ATP. Magnesium plays a key role in carbohydrate metabolism. Magnesium may influence the release and activity of hormones that control blood glucose level via tyrosine kinase. Insulin dependent absorption of glucose requires magnesium.

Mohammad Keshvri Delavan et al., found that mean of magnesium, zinc in mothers of both group (gestational diabetic group & non diabetic pregnant women) had no significant difference. GDM group showed mean zinc 67.44 +_ 12.1, compared to normal group 73.34 +- 10.8, with p- value of 0.11 and found no significant difference between serum zinc level in GDM and normal group. Mean magnesium in GDM group was 1.84 +- 0.15, whereas mean magnesium in normal group was 1.86 +- 0.10, with p - value 0.71, it is not significant [16].

Farideh Akhlaghi et al., found in their study that there was no significant difference between GDM and normal control group in serum zinc and magnesium level [11].

The observation of Emmanuel I. Ugwuja was that low serum zinc level in diabetic pregnant women may be due to hyperexcretion of zinc in urine [12].

Fadia Mahmoud et al., also concluded that lower level of magnesium is seen in normal pregnancy compared to non-pregnant women. The p - value is < 0.01 . Significant [14].

Sunita Pujar et al., found that level of serum zinc and magnesium was statistically significantly decreased in diabetes mellitus patients compared to healthy controls. Mean zinc in control group was 89.61 +- 27.74, whereas mean zinc in diabetes mellitus group was 67.50 +- 13.85. Similarly mean magnesium was lower in diabetes mellitus group compared to normal control group. mean magnesium in control group was 2.43 +- 0.42, mean magnesium in DM group was 2.01 +- 0.39, (p - value ; < 0.001), highly significant [15].

The observation of P. Ertbeg et al was that the level of ionized magnesium was statistically significantly elevated in patients with gestational diabetes compared to controls. Mean magnesium in GDM group was 0.57 +- 0.05 mmol / L, but in control group mean magnesium was 0.51 +- 0.06 mmol / L, P - value is significant (< 0.01) [30].

In the present study 30 women with primi GDM were taken as GDM group and 30 women with normal primi who were age and BMI matched as control group. The study was done between 24 to 28 weeks of pregnancy as the diabetogenic tendency is maximum after second trimester or pregnancy due to the peaking of placental hormones which is done similar to the studies by Farideh Akhlaghi et al [11] .

The current study inferred that the mean concentration of zinc was statistically lower in GDM group as compared to controls. The mean zinc concentration in the GDM group was 59.61 µg / dl. The mean zinc level in control group was 69.07 µg / dl. In GDM group, an increased occurence of zinc deficiency was observed in this study. It is unknown whether reduction in serum zinc concentration is a predisposing factor for GDM or pregnant women with hyperglycemic status have low serum zinc levels. Mean concentration of magnesium was lower in GDM group as compared to controls, but it was not statistically significant. The mean magnesium concentration in the GDM group was 1.69 mg /dl, the mean magnesium level in control group was 1.74 mg / dl.

In current study, 90% of women with GDM showed zinc deficiency and women with normal OGTT showed 63% zinc deficiency. The decreased level of zinc during pregnancy may be due to increased demand

and low absorption of zinc from duodenum in the presence of calcium, iron. The deficiency of zinc in GDM may be due to hyperzincuria.

RELATIONSHIP BETWEEN ZINC AND OTHER VARIABLES:

In the current study, zinc level was correlated with different parameters like age, BMI, diet, residence among the GDM group.

Age and Zinc Levels:

The mean level of zinc between 20 to 25 years of age was 58.51 µg / dl, and the mean level of zinc between 26 to 30 years was 66.80 µg / dl. The p - value obtained was 0.219 and found to be not significant.

BMI and Zinc Level:

In the present study, women with normal BMI were included. As obesity itself is found to increase the chance of developing GDM, obese women were excluded from the study. The mean BMI in GDM group was 23.50 kg / ^{m2}. The mean zinc level was 60.78 µg / dl in women with normal BMI and 52.02 µg / dl in women with overweight, and the p - value was found to be significant (0. 039).

Family history of diabetes and Zinc Level:

Mean zinc in GDM group with positive family history of diabetes was 56.95 µg / dl. Mean zinc in GDM group with no family history of diabetes mellitus was 61.65 µg / dl, mean zinc level was higher in GDM group with no family history of diabetes than GDM group with positive family history, but the p - value is not statistically significant (p : 0.113).

Residence and Zinc Level:

There were 8 out of 30 subject with GDM from rural areas and remaining 22 subjects of GDM group were from urban areas. Mean zinc in subjects with urban residence was 59.81 µg / dl and mean zinc in subjects with rural residence was 59.06 µg / dl. The p - value is 0.824 There is slight decrease in mean zinc level in subjects with rural residence, but it was not statistically significant.

Diet and Zinc Level:

Mean zinc level in non-vegetarian GDM group was 59.23 µg / dl , and mean zinc in vegetarian GDM group was 63.03 µg / dl. P value - 0.446. Mean zinc level was slightly higher in vegetarian group, but it was not statistically significant.

RELATIONSHIP BETWEEN MAGNESIUM AND OTHER VARIABLES

Age and Magnesium Level:

The mean level of magnesium between 20 to 25 years of age was 1.75 mg / dl and between 26 to 30 years was 1.34 mg / dl. The mean magnesium was lower in higher age group. p value was 0.103, it was not statistically significant.

BMI and Magnesium Level:

Mean magnesium level was 1.69 mg / dl in women with normal BMI and in women with overweight GDM group was 1.75 mg / dl and the p - value was 0.714, not statistically significant. There was no significant difference between these two groups.

Family history of diabetes and Magnesium Level:

Mean magnesium level in GDM group with positive family history of diabetes mellitus was 1.77 mg / dl. Mean magnesium level in GDM group with no history of diabetes was 1.64 mg / dl. It is higher in women with GDM group of positive family history.

Residence & Magnesium Level :

Mean magnesium level in subjects of GDM group with urban residence was 1.77 mg / dl, whereas mean magnesium in subjects of GDM group with rural residence was 1.50 mg / dl. The mean magnesium level was lower with subjects in rural areas. The cause could be an inadequate intake of magnesium rich food.

Diet and Magnesium Level:

Mean of magnesium in vegetarian GDM group was 1.96 mg /dl , and in non-vegetarian GDM group was 1.67mg / dl, P value - 0.151. There is no significant difference in magnesium level in both groups.

SUMMARY

SUMMARY

- Micronutrients of zinc and magnesium status was assessed in GDM primigravida - women in GDM group had lower zinc levels.
- The mean serum zinc level in GDM group was estimated and was 59.61 µg / dl.
- The mean serum zinc concentration in control group (primigravida with normal blood glucose level) was estimated and was 69.07 µg / dl.
- The zinc levels in GDM group were statistically lower as compared to control group (p : 0.000).
- The mean magnesium in GDM group was estimated and was 1.69 mg / dl, The mean serum magnesium concentration in control group was 1.74 mg / dl. The magnesium levels in GDM were lower but not statistically significant.
- Correlation between blood glucose levels and zinc was - 0.226 and correlation between glucose and magnesium was - 0.058. Micronutrient concentration were negatively correlated with blood sugar.

CONCLUSION

CONCLUSION

Diabetes mellitus occurs throughout the world, especially type 2 diabetes. The increase in incidence in developing countries like India follows the trend of urbanization and lifestyle changes, including increasingly sedentary lifestyles, less physically demanding work and the global nutrition transition, marked by increased intake of foods that are high energy dense but nutrient poor. The risk of getting type 2 diabetes has been widely found to be associated with lower socioeconomic status. Gestational diabetes mellitus is a strong predictor of postpartum diabetes and transition to overt type 2 diabetes in later life. So identification of GDM is a major health concern in the society.

Pregnancy itself is a state of insulin resistance. Women who develops GDM is partly due to insulin resistance and partially due to inadequate insulin secretion. Zinc is a essential element for insulin secretion. Magnesium is also essential for insulin action. Zinc and magnesium deficiency is one of the preventable risk factor of diabetes mellitus. This has important health implications for diabetic pregnant women and their newborns. From the current study it is found that serum zinc levels were significantly less in women with GDM compared to women with normal pregnancy and the amount of magnesium in women with gestational diabetes mellitus was less than control group, but it was not statistically significant. It may be due to the duration of disease and serum

magnesium level may be normal even when intracellular magnesium is deficient.

Diabetes mellitus is a major public health problem throughout the world and is growing in populations, therefore should be more attention to be paid on the concentrations of microelements in pregnant women and screening for zinc, magnesium level in pregnancy is essential. Supplementation of zinc, magnesium and encouraging them to eat zinc and magnesium rich food may play a pivotal role in decreasing the incidence of GDM and diabetes mellitus in future.

LIMITATIONS

1. In this study food intake diary was not included. Dietary intake and supplementation of multivitamins were also important.
2. No data about preterm serum zinc, magnesium levels
3. Further studies with micronutrient substitution and glycemic control in GDM would strongly help in revealing influence of zinc & magnesium in glucose homeostasis.

FUTURE SCOPE

The current study could be of public health importance as antenatal screening for serum micronutrient status and proper supplementation of zinc, magnesium may prevent development of gestational diabetes mellitus, control the hyperglycemic status and may reduce the risk of spontaneous preterm birth and other fetal complications.

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ANNEXURES

CONSENT FORM

Dr.M.Jeyalakshmi,post graduate student in the Department of Physiology, Coimbatore Medical College,Coimbatore is conducting a study on " A COMPARATIVE STUDY OF MICRONUTRIENT STATUS IN GESTATIONAL DIABETICS AND NORMAL PRIMIGRAVIDA " . The study and test procedures were explained to me clearly. I hereby give my Consent to participate in this study, and to give blood sample. The data Obtained herein may be used for research and publication.

Place:

Date: Signature of the patient

(Name :)

ஒப்புதல் படிவம்

பெயர் வயது

பாலினம்

முகவரி

அரசு கோவை மருத்துவக்கல்லூரியில் உடல் இயக்கத் துறையில் பட்ட மேற்படிப்பு பயிலும் மாணவி மரு. M.ஜெயலெட்சுமி அவர்கள் மேற்கொள்ளும் "கர்ப்பகால நீரிழிவு இடையே உள்ள நுண்ணூட்ட ஒப்பீட்டு" ஆய்வின் செய்முறை தொடர்பான அனைத்து விபரங்களையும் கேட்டு எனது சந்தேகங்களைத் தெளிவுபடுத்தி கொண்டேன்.

நான் இந்த ஆய்வில் என்னை பரிசோதனை செய்ய முழு மனதுடனும், சுயசிந்தனையுடனும் சம்மதிக்கிறேன்.

என்னை பற்றிய அனைத்த விபரங்களும் பாதுகாப்பதுடன், இதன் முடிவுகள் ஆய்விதழில் வெளியிடப்படுவதில் ஆட்சேபனை இல்லை என்பதைத் தெரிவித்துக் கொள்கிறேன். எந்த நேரத்திலும் இந்த ஆய்விலிருந்து நான் விலகிக் கொள்ள எனக்கு உரிமை உண்டு என்பதையும் அறிவேன்.

இடம் : நோயாளியின் கையொப்பம்

நாள் :

PROFORMA

ID No :

Name :

Age / Sex :

Place :

Occupation :

LMP : EDD :

Height : Weight :

BMI :

Pulse Rate : BP :

History of Presenting Illness:

Past History :

Family History of Diabetes

Mellitus : Present / Absent

Personal History : Vegetarian / Non Vegetarian

General Examination :

Systemic Examinations : CVS / RS / CNS

Investigation done already :

75gm OGTT

USG Report

Serum Zinc level :

Serum Magnesium level :

MASTER CHART

Serum Zinc, Magnesium Level in GDM Group

S.No	Name	Group	Age	G/w	Ht	Wt	BMI	OGTT	Zn	Mg	F/H	RES	DIET
1	Sudha	Case	22	25	146	53	24.86	147	54.5	1.87	A	U	NV
2	Kowsalya	Case	21	23	156	69	28.35	162	52.9	1.41	P	R	NV
3	Sindhu	Case	22	24	142	48	23.8	146	57.8	1.92	A	U	NV
4	Sharmila Mary	Case	22	23	153	47	20.08	144	59.2	1.64	A	R	NV
5	Anandhi	Case	23	24	158	56	22.43	151	61.3	1.83	P	U	V
6	Durgadevi	Case	20	25	147	55	25.45	156	50.8	1.98	P	U	NV
7	Sivagami	Case	24	23	160	58	22.66	148	67.5	1.4	A	R	NV
8	Krithiga	Case	21	22	153	53	22.64	147	68	1.97	P	U	NV
9	Thangamani	Case	20	26	159	61	24.13	174	53.2	1.99	P	U	NV
10	Malathi	Case	22	20	156	57	23.42	149	61.9	1.89	A	U	NV
11	Sheela	Case	20	24	155	53	22.06	147	50.4	1.93	A	U	V
12	Indhu	Case	20	23	147	53	24.53	156	51.2	1.88	P	U	NV
13	Saraswathi	Case	24	22	151	49	21.49	151	55.7	2.05	A	R	NV
14	Shalini	Case	23	25	148	60	27.39	148	52.8	1.61	P	U	NV
15	Suganya	Case	22	20	154	62	26.14	143	51.6	2.03	P	R	NV
16	Nagavalli	Case	24	23	157	56	22.72	144	58.3	1.43	P	U	NV
17	Sunitha	Case	26	22	156	58	23.83	159	64.1	1.12	A	U	NV
18	Gunavathi	Case	23	24	158	58	23.23	146	73.3	1.87	P	U	NV
19	Priiya	Case	22	23	154	56	23.61	143	57.5	1.08	A	R	NV
20	Deviga	Case	21	22	149	55	24.77	170	59.4	1.34	A	R	NV
21	Subeena	Case	23	24	150	53	23.56	141	77.4	2.13	A	U	V
22	Divya	Case	20	25	148	51	23.28	143	54.5	1.87	P	U	NV
23	Lalitha	Case	29	22	161	57	21.99	150	81.9	1.88	A	U	NV
24	Banu	Case	22	27	158	54	21.63	156	53.2	1.99	A	U	NV
25	Amudha	Case	27	23	147	52	24.06	148	56.8	1.23	P	U	NV
26	Nithya	Case	23	24	148	49	22.37	144	59.7	1.57	A	U	NV
27	Pavithra	Case	28	20	146	50	23.46	149	64.4	1.14	A	U	NV
28	Shanthi	Case	21	23	156	52	21.37	153	68.7	1.07	A	R	NV
29	Subaitha	Case	20	24	157	53	21.5	146	54.8	1.87	A	U	NV
30	Swetha	Case	23	22	149	54	24.32	163	55.7	1.99	P	U	NV

G/W - gestational week, Ht - height, Wt - weight, BMI - body mass index, OGTT - oral glucose tolerance test, Zn- Zinc, Mg - Magnesium,
F/H - Family History, RES - Residence, P - Present, A - Absent, R - Rural, U -Urban, V - Vegetarian, NV - Non vegetarian

Serum Zinc, Magnesium Level in Normo Glycemic Primi

S.No	Name	Group	Age	G/w	Ht	Wt	BMI	OGTT	Zn	Mg	F/H	RES	DIET
1	Manjula	Control	20	24	156	56	23.01	117	83.4	1.4	A	U	V
2	Nandhini	Control	20	26	158	57	22.83	114	76.1	1.11	A	U	NV
3	Kavitha	Control	20	25	159	58	22.94	115	57.8	1.93	A	U	NV
4	Maheswari	Control	25	23	147	53	24.53	120	59.2	1.65	A	U	NV
5	Muthumanimegalai	Control	21	24	152	55	23.8	124	64.5	1.82	A	R	NV
6	Logeshwari	Control	20	26	153	54	23.07	119	78.8	2.3	A	U	NV
7	Sathyaselvi	Control	22	24	161	55	21.22	126	70.3	1.67	P	U	V
8	Nithya	Control	24	20	158	50	20.03	114	73.4	1.8	A	U	NV
9	Bagyalakshmi	Control	20	22	163	53	19.95	125	67.4	1.89	A	U	NV
10	Meena	Control	23	24	154	51	21.5	127	89.1	1.27	A	U	NV
11	Radhika	Control	25	23	155	52	21.64	122	94.7	2.11	P	R	NV
12	Maniselvam	Control	26	21	157	53	21.5	117	73.2	1.87	A	R	V
13	Lavanya	Control	21	22	164	53	19.71	118	61.3	1.98	P	R	NV
14	Kannammal	Control	24	25	158	54	21.63	123	64.5	1.99	A	U	NV
15	Lakshmi	Control	22	20	154	50	21.08	131	65.7	1.89	A	U	V
16	Sangeetha	Control	23	20	156	49	20.13	119	61.9	1.93	P	U	NV
17	Kalaivani	Control	27	24	153	52	22.21	134	70.8	2.05	A	U	NV
18	Jeeva	Control	22	27	164	59	21.94	126	59.3	1.43	P	U	NV
19	Kani	Control	21	28	152	57	24.67	114	66.8	1.87	P	U	NV
20	Saranya	Control	23	22	148	53	24.2	109	62.3	1.89	A	U	NV
21	Vanitha	Control	24	23	153	54	23.07	116	66.3	1.76	A	R	NV
22	Mahalakshmi	Control	21	24	165	57	20.94	130	66.7	1.46	A	U	NV
23	Ramadevi	Control	20	25	151	53	23.24	128	57.5	1.23	A	U	V
24	Anitha	Control	20	21	155	54	22.48	126	61.2	1.47	A	U	NV
25	Geetha	Control	23	24	152	49	21.21	127	63.5	2.6	A	R	NV
26	Deivanayaki	Control	26	22	160	52	20.31	114	91.1	1.57	A	U	NV
27	Indirani	Control	24	20	154	54	22.77	115	88.7	1.77	A	U	NV
28	Jayanthi	Control	22	25	157	56	22.72	121	58.5	1.53	A	U	NV
29	Nandhini	Control	22	26	147	51	23.6	127	57.5	1.83	A	U	NV
30	Devi	Control	20	23	150	53	23.56	118	60.8	1.14	A	U	NV

G/W - gestational week, Ht - height, Wt - weight, BMI - body mass index, OGTT - oral glucose tolerance test, Zn- Zinc, Mg - Magnesium,
F/H - Family History, RES - Residence, P - Present, A - Absent, R - Rural, U -Urban, V - Vegetarian, NV - Non vegetarian